The New England
Journal of Medicine

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VOLUME 223 JULY 18, 1940 NUMBER 3

CYSTOURETHROGRAMS

Roentgen Visualization of the Urethra, Bladder and Prostate

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ACCURATE estimation of the size of the obstructing prostate is difficult. Rectal examination alone enables one to feel that portion of the enlarged gland which lies posteriorly, but does not necessarily give information regarding tissue which narrows the urethral lumen. Cystoscopic examination is likewise often misleading, for although intravesical protrusions of the prostate can be seen, it is frequently impossible to estimate accurately the size of the obstructing lobes. Degrees of intraurethral enlargement of the prostate are best gauged by examination with the panendoscope, but such investigations in elderly, debilitated patients are not only unpleasant but carry with them the danger of hemorrhage and infection. A more accurate estimation of the size and character of the obstructing gland, we believe, can be obtained by cystourethrograms than by cystoscopic and rectal examination, with less risk, discomfort and indignity to the patient.

FIGURE 1. *Normal Bladder and Urethra (cystourethrogram).*

The bladder is outlined by air, and the urethra filled with tragacanth-Lipiodol emulsion. The verumontanum and external and internal sphincters are outlined.

The increasing use of transurethral methods for relieving prostatic obstruction makes necessary a more accurate knowledge of the size of the prostate, since transurethral resection is best suited to glands of moderate size. Prostates weighing over 60 or 70 gm., we believe, are usually best treated by open operation, that is, suprapubic or perineal enucleation. Gross overestimation or underestimation of the size of the obstructing prostate has been a common experience with us and others. Any means by which the size and type of obstruction can be more nearly approximated will aid in the selection of the most suitable type of operation.

Roentgen visualization of the urethra, bladder and prostate is of recent development. In 1933 Flocks[1] discussed its advantages and described the technic that we now use. The information obtained by this method has enabled us to judge more accurately the size of the prostate and the type of enlargement, and has made cystoscopic examination, with its disagreeable features, unnecessary in many cases of prostatic obstruction. It has helped us select the cases best suited to transurethral removal of the prostate. Cystourethrograms have provided valuable information in many other conditions, such as stricture, prostatic abscess and tumors of the pelvis.

The technic of this procedure is not difficult, and the apparatus is simple. The following are necessary: a soft-rubber catheter, No. 16 or 18 Fr.;

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FIGURE 2. *Case 1. Diverticulum of the Bladder and Fibrous Contraction of the Bladder Outlet: Complete urinary retention (sodium iodide cystogram).*

There is a large diverticulum on the right, and a small bladder shadow on the left, with an irregular, trabeculated wall due to obstruction at the bladder outlet.

FIGURE 3. *Case 1. Diverticulum of the Bladder and Fibrous Contraction of the Bladder Outlet: Complete urinary retention (cystourethrogram).*

The large diverticulum is outlined by air; the small contracted bladder is filled with the emulsion. Note the small bladder neck due to the fibrous contraction frequently associated with diverticulums and infection.

FIGURE 4. *Case 2. Early Benign Hypertrophy of the Prostate (sodium iodide cystogram).*

There is a round, smooth-walled bladder without evidence of long-standing obstruction. The multiple small calculi that sometimes accompany early hypertrophy of the prostate are evident.

FIGURE 5. *Case 2. Early Benign Hypertrophy of the Prostate (air cystogram).*

The intravesical protrusion of the median lobe of the prostate stands out in contrast to the air-filled bladder.

FIGURE 6. *Case 2. Early Benign Hypertrophy of the Prostate (cystourethrogram).*

There is anterior bending of the prostatic urethra, characteristic of median-lobe enlargement, and a widened shadow of the prostatic urethra due to intraurethral lateral-lobe enlargement compressing the urethra. Transurethral resection was performed, with removal of 9 gm. of tissue.

FIGURE 7. *Case 3. Benign Hypertrophy of the Prostate (sodium iodide cystogram).*

The patient was a seventy-one-year-old man with well-advanced changes from urinary obstruction. There is an irregular bladder outline due to trabeculation, and a reflux up the ureter, with an incompetent ureterovesical valve.

FIGURE 8. *Case 3. Benign Hypertrophy of the Prostate (air cystogram).*

The large median lobe of the prostate bulges into the bladder cavity.

FIGURE 9. *Case 3. Benign Hypertrophy of the Prostate (cystourethrogram).*

There is an enlarged median lobe with anterior bowing of the urethra, and a widened prostatic urethra due to intraurethral lateral lobes. Transurethral resection resulted in the removal of 26.5 gm. of prostatic tissue. This is a more advanced stage of prostatic hypertrophy than is that seen in Case 2.

FIGURE 10. *Case 4. Benign Hypertrophy of the Prostate (cystourethrogram).*

There is well-marked intravesical enlargement of the median and lateral lobes,—the "collar type" of hypertrophy,—with only slight intraurethral lateral-lobe enlargement; 33.5 gm. of tissue were removed by transurethral resection.

FIGURE 11. *Case 4. Benign Hypertrophy of the Prostate (cystourethrogram after transurethral resection).*

There is a wide-open bladder neck, with complete relief of retention.

FIGURE 12. *Case 5. Benign Hypertrophy of the Prostate (cystourethrogram).*

This represents the median-bar type of obstruction, with some anterior bowing of the urethra and a small filling defect. The retention was relieved by the removal of 3 gm. of tissue.

FIGURE 13. *Case 6. Benign Hypertrophy of the Prostate (cystourethrogram).*

This shows median-lobe enlargement only. There is anterior bowing of the urethra but no spreading to denote intraurethral-lobe enlargement.

FIGURE 14. *Case 7. Benign Hypertrophy of the Prostate (cystourethrogram).*

There is moderate intravesical enlargement of the median and lateral lobes; 31 gm. of tissue were removed by transurethral resection.

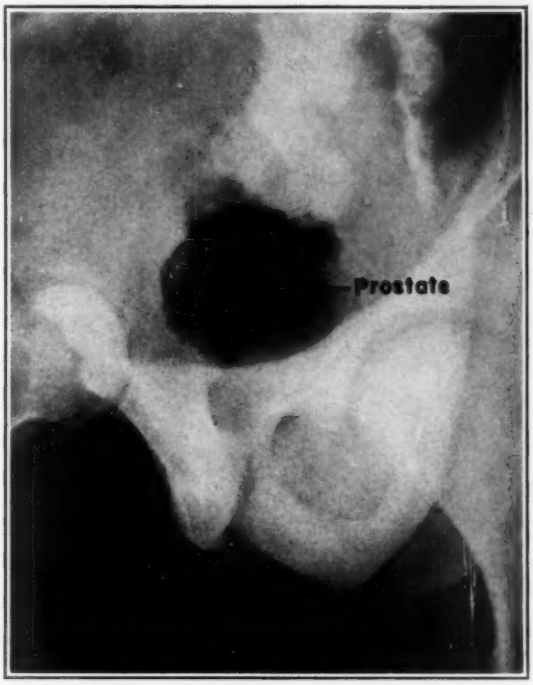

FIGURE 15. *Case 8. Benign Hypertrophy of the Prostate (air cystogram).*

The enlarged median and lateral lobes protrude into the bladder cavity.

FIGURE 16. *Case 8. Benign Hypertrophy of the Prostate (cystourethrogram).*

There is marked anterior bowing of the urethra due to the enlarged median lobe, with considerable widening of the urethra due to compression by the lateral lobes. From rectal examination and the cystoscopic appearance this prostate was considered too large for resection. The cystourethrogram showed only moderate enlargement, however, and 23 gm. of tissue were removed by transurethral resection, with relief of retention.

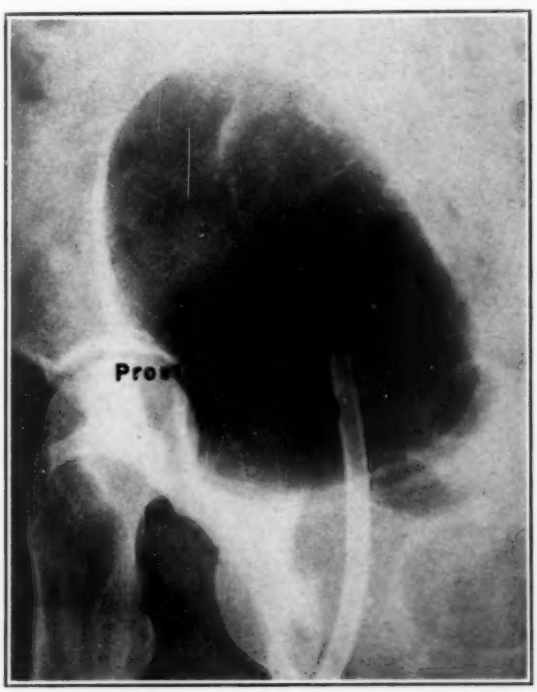

FIGURE 17. *Case 9. Carcinoma and Benign Hypertrophy of the Prostate (air cystogram).*

There is advanced cancer of the posterior lobe, with metastasis to the ischium; also, marked benign intravesical enlargement of the lateral lobes, with but little median-lobe hypertrophy.

FIGURE 18. *Case 9. Carcinoma and Benign Hypertrophy of the Prostate (cystourethrogram).*

There is marked spreading of the urethra from intraurethral and intravesical enlargement of the lateral lobes; 33.5 gm. of tissue were removed by transurethral resection, with relief of retention.

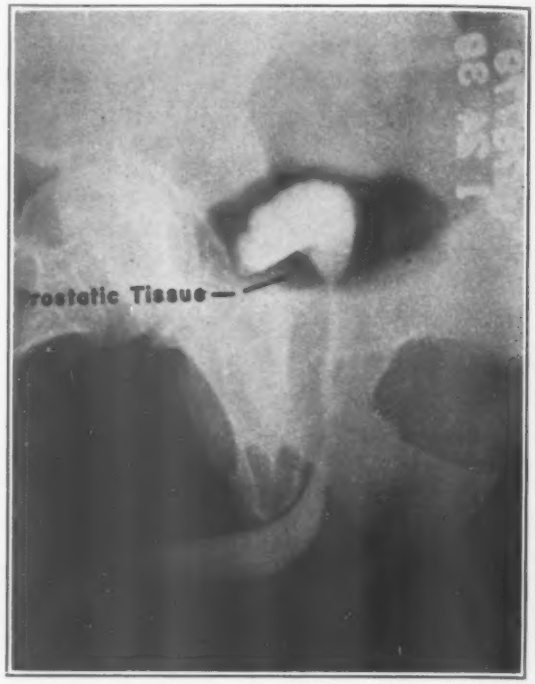

FIGURE 19. *Case 10. Benign Hypertrophy of the Prostate (cystourethrogram).*

There is prostatic tissue at the anterior commissure, remaining after resection elsewhere. Considerable urinary retention was relieved by the removal of 4.5 gm. of tissue.

FIGURE 20. *Case 11. Carcinoma of the Rectum (cystourethrogram).*

This represents a case with contracture of the bladder outlet and urinary retention after combined abdominoperineal operation for carcinoma of the rectum. The air-filled bladder shows the typical deformity following such operations, with the bladder base falling back toward the sacrum. Retention was relieved by the transurethral removal of 1 gm. of fibrous tissue from the bladder neck and small intraurethral lateral lobes.

FIGURE 21. *Case 12. Periurethral Abscess (cystourethrogram).*

The normal bladder is filled with air. There is an irregular defect in the bulb from abscess, with a small perineal fistula.

one 50-cc. glass syringe, with a 7.5-cm. section of catheter securely fastened to the adapter; a 90-cc. Asepto glass syringe; sodium iodide, 3 per cent solution; and a tragacanth-Lipiodol emulsion.*

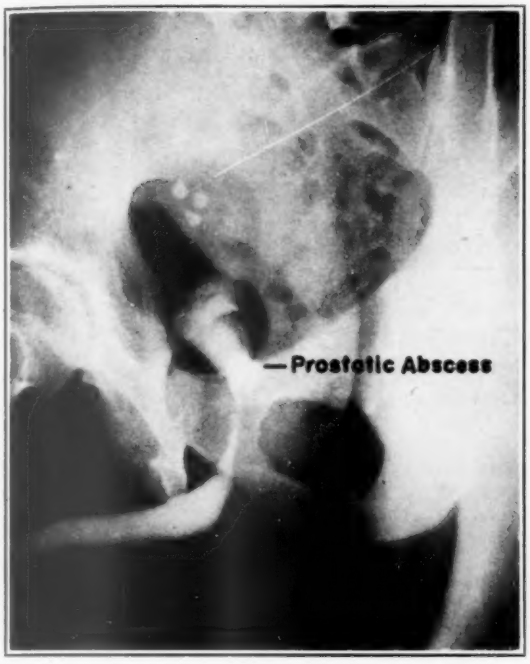

FIGURE 22. *Case 13. Tuberculosis of the Prostate (cystourethrogram).*

The bladder is small and contracted. There is a large cavity in the prostatic urethra due to an old tuberculous abscess.

FIGURE 23. *Case 14. Chondrosarcoma of the Pelvis (cystourethrogram).*

The urethra is distorted and displaced by a huge pelvic tumor.

With the patient on his back on the x-ray table, a plain roentgenogram is taken of the pelvis. A catheter is passed to the bladder, and the amount of residual urine is determined. The bladder is filled to capacity with a 3 per cent solution of sodium iodide, and an anteroposterior exposure is made. The solution is washed out with sterile distilled water. The patient is then turned at a 45° angle with the table, the underneath right leg is flexed and the uppermost left leg extended. The bladder is filled with air through the catheter with the Asepto syringe, and another exposure is taken. About 30 cc. of the air is removed with the syringe, and the urethral catheter is withdrawn. At the same time the urethra is closed at the meatus with the thumb and finger of the left hand to prevent the escape of the remaining air from the bladder. The 50-cc. glass syringe filled with the emulsion is taken in the right hand, and the short length of the urethral catheter is inserted into the urethra. The emulsion is slowly injected, and as the last of it leaves the syringe the final roentgenogram is taken with the patient still in the oblique position. The emulsion is washed out of the bladder, using distilled water injected by the Asepto syringe through the catheter.

Four roentgenograms are thus taken. The plain anteroposterior exposure shows the pelvic bones and vesical or prostatic calculi. The picture taken with the bladder filled with sodium iodide solution outlines the bladder wall, defines diverticulums, makes evident any regurgitation up the ureters from incompetent ureteral valves and detects the filling defects of large vesical neoplasms. The air cystogram taken in the oblique position affords a contrast for solid tissue projecting into the bladder cavity, and very clearly shows intravesical protrusions of the enlarged prostate. The combined cystourethrogram visualizes the entire urethra bladder neck and prostate, and shows the caliber of the anterior urethra and the deformities of the posterior urethra that result from intra-

*The emulsion is made up as follows:

Powdered gum tragacanth	25 gm.
Ethyl alcohol (95 per cent)	40 cc.
Distilled water	660 cc.

This mixture is kept in an icebox overnight, and autoclaved for ten minutes the following day. Two hundred and fifty cubic centimeters of the jelly should be mixed with 60 cc. of Lipiodol. Enough sterile water is added to the mixture to give a viscosity equal to that of ordinary lubricating jelly. The emulsion should be kept for use in 50-cc. amounts in small, sterile flasks.

urethral enlargements of the prostate. The bladder neck is plainly enough outlined to detect the changes due to bars or contractures. The contrast between the air-filled bladder and the lobes of the enlarged prostate, as outlined by the tragacanth-Lipiodol solution, gives a striking picture of the size and character of the obstructing gland.

With a little experience it is easy to interpret the roentgenograms. They illustrate the configuration of the normal urethra and bladder, and the distortions produced by most of the different forms and degrees of prostatic obstruction.

SUMMARY

Visualization of the urethra, bladder and prostate by cystourethrograms is helpful in estimating the type and degree of prostatic obstruction. It is an aid in the selection of the type of operation best suited to the patient, that is, transurethral removal or open enucleation. In many other conditions it provides valuable information concerning disease of the genitourinary organs.

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VITAMIN A REQUIREMENTS IN RHEUMATOID ARTHRITIS*

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BOSTON

A GREAT deal of attention has been paid to the diet of the arthritic patient during the past few years. Bauer[1] has suggested that a high-vitamin, high-caloric diet, with adequate amounts of calcium, phosphorus and iron and normal proportions of carbohydrates, proteins and fats, should be the diet of choice for routine use. Despite controversy that is still carried on regarding the amounts of carbohydrate, fat and protein that should be fed to an arthritic patient, there is unanimity of opinion regarding the value of a high-vitamin diet in arthritis.[2]

The identification of certain vitamins by chemical and biological methods has made possible studies concerning the relation of their specific effects to arthritis. No definite deficiency in vitamin B in rheumatoid arthritis has been demonstrated,[3] but Steinberg[4] found that the gastrointestinal symptoms in 105 rheumatoid arthritic patients were alleviated by moderate dosage of vitamin B complex; no effect on the arthritis was noted. Abrams and Bauer[5] believe that in rheumatoid arthritis the usual therapeutic doses of vitamin D will give generally desired results, without the danger and expense of massive dosage. Hall, Darling and Taylor[6] and others[7] showed that 75 per cent of rheumatoid arthritic patients had a subnormal content of vitamin C in the blood. The administration for eight months of a known satisfactory dose of this substance failed to produce a salutary effect in a large group of patients.

The relation of a low vitamin A level to rheumatoid arthritis has been suggested by Race,[3] who studied the plasma vitamin A and the carotinoid pigments in rheumatic patients by means of the light-extinction density. He found the lowest value given by patients with rheumatoid arthritis.

The present studies were undertaken in order to determine the distribution of vitamin A values among patients with rheumatoid arthritis as compared with normal individuals on a similar dietary regime. At the same time, information was sought as to the daily requirement of vitamin A in the same patients and to determine the effect, if any, on the course of the disease when this requirement was fulfilled.

Direct chemical and spectrographic methods for the determination of vitamin A have been suggested.[8, 9] The former cannot be considered to be a specific and quantitative method, and the latter is still in the investigative stage.[10] Bloch[11] first suggested that loss of visual acuity in dim light is related to vitamin A deficiency. Wald[12] has shown that in mammals and other animals vitamin A unites with a protein in the retina to form visual purple. This process takes place continuously and is dependent on a sufficient supply of vitamin A. In addition, this author suggested that the rate of formation of visual purple after the exposure of the retina to bright light is dependent on the available supply of vitamin A.

*From the Medical Service of the Robert Breck Brigham Hospital, Boston. The expenses of this investigation were defrayed in part by a grant from the Smith, Kline & French Laboratories, Philadelphia.

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The increasing ability to see in dim illumination after exposure to bright light has been called dark adaptation, and the measurement of this function has been the basis for methods used for the indirect evaluation of vitamin A deficiency.[13, 14]

Method

In measuring the dark-adaptation curve we have used the biophotometer* as described by Jeans, Blanchard and Zentmire.[13] The satisfactory use of this apparatus in estimating vitamin A deficiency has been confirmed by Jeghers[15] and others.[16]

After an initial period of ten minutes in darkness the subject was exposed to a standardized bright light for three minutes, to exhaust partially the visual purple in the cells of the retina. The dark-adaptation curve was then measured, and readings were taken every two and a half minutes up to ten minutes following the end of the exposure to bright light. For this study we used the initial reading, taken twenty seconds after the end of the bright-light exposure, as an index of the normal or abnormal dark adaptation, and related this reading to vitamin A metabolism.

Seventy-nine patients (Group A) with radiological evidence of rheumatoid arthritis in one or more joints or fusiform polyarthritis of over six months' duration were utilized. No patient had an obvious focus of infection. For the most part the patients studied were afebrile or had the usual temperature fluctuations — 98 to 100°F. — found in chronic arthritis. Known gastrointestinal or hepatic dysfunction was absent. Intraocular disease, which would have interfered with the test, was ruled out in every case. Those patients who wore glasses for refractive errors used them in the test. None had received specific vitamin A therapy recently, and the diets varied from the sparse one of the indigent, ambulatory outpatient to the well-rounded diet received by the ward patient. The 13 controls were student nurses and hospital attendants and were young adults, all of whom ate the regular hospital diet. For the purpose of determining the incidence of vitamin A deficiency each individual was tested biophotometrically.

By the technic described above, all the controls gave initial biophotometer readings of less than 0.50 millifoot candles. In addition, all patients receiving adequate vitamin A therapy eventually gave and maintained readings under this same figure. For these reasons we have arbitrarily used 0.50 millifoot candles as the upper limit of the normal range.

*Manufactured by the Frober–Fayber Company, Cleveland, Ohio.

We were able to study 13 arthritic patients (Group B) for long enough time to determine the amount of vitamin A needed per day to give and maintain normal dark-adaptation curves. These patients were selected from Group A, and all had shown definite abnormal dark adaptation when first tested. They were tested at weekly intervals while receiving increasing supplemental doses of vitamin A (halibut-liver oil). Initially, a dose of three capsules (25,500 U.S.P. units) a day was given. This dose was increased by one capsule per day if after two weeks no improvement in the initial reading of the dark-adaptation curve had occurred, or if after one week there was a change in the initial reading to a more abnormal level. This regime was continued until the initial biophotometer reading was maintained at or below 0.50 millifoot candles. In these patients the erythrocytic sedimentation index[17] and the hemoglobin concentration were determined at weekly intervals.

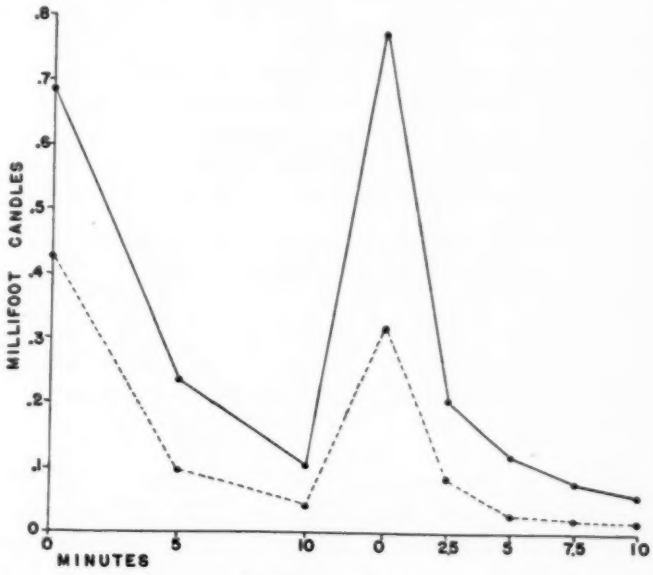

Figure 1.

The dotted line is the average of the dark-adaptation curves of thirteen controls; the solid line that of seventy-nine patients with rheumatoid arthritis.

In 45 cases the simultaneous initial biophotometer readings and erythrocytic sedimentation indices were correlated.

Results

The average initial biophotometer reading of the 79 patients with rheumatoid arthritis was 0.78 millifoot candles and that of the controls was 0.32 millifoot candles. The difference between the average of the curves of dark adaptation for the patients and for the controls is shown in Figure 1.

Twenty-eight (35 per cent) of the 79 patients in Group A had initial readings at or below the normal limit of 0.50 millifoot candles. The same number had initial readings between 0.50 and 1.00 millifoot candles and were considered borderline or subnormal. Seventeen patients (21 per cent) fell between 1.00 and 1.50 millifoot candles. This we consider a moderate impairment of dark adaptation, indicating moderate vitamin A deficiency. The remaining 6 patients (9 per cent) in Group A had initial readings greater than 1.50 millifoot candles and were considered severely deficient in vitamin A. All but 2 of the patients of these last two sub-groups were receiving the regular hospital diet. The average of the readings of the dark-adaptation curves for the controls and for the 79 patients with rheumatoid arthritis are shown in Table 1. The patients are divided in this table into four groups, as described above, according to the deviation of their initial biophotometer readings from the normal range.

TABLE 1. *Average Dark-Adaptation Curves of Controls and of 79 Unselected Cases of Rheumatoid Arthritis.*

Group	No. of Cases	Range of Initial Biophotometer Readings	Probable Vitamin A Deficiency	Average Biophotometer Readings				
				Initial	2½ min.	5 min.	7½ min.	10 min.
		mft. cand.		*mft. cand.*	*mft. cand.*	*mft. cand.*	*mft. cand.*	*mft. cand.*
Controls	13	0.18–0.47	None	0.32	0.09	0.03	0.02	0.02
Rheumatoid arthritis patients	79	0.13–1.95		0.78	0.21	0.12	0.08	0.05
Subgroup 1	28	0.13–0.47	None	0.35	0.10	0.05	0.02	0.01
Subgroup 2	28	0.55–0.97	Borderline	0.76	0.22	0.12	0.08	0.06
Subgroup 3	17	1.00–1.48	Moderate	1.20	0.27	0.18	0.12	0.07
Subgroup 4	6	1.55–1.95	Severe	1.69	0.38	0.17	0.11	0.08

TABLE 2. *Relation of Age of Rheumatoid Arthritic Patients to Initial Biophotometer Readings.*

Age Range	No. of Cases	Average Initial Biophotometer Reading
yr.		*mft. cand.*
10–19	3	0.63
20–29	21	0.63
30–39	14	0.62
40–49	26	0.83
50–59	11	1.05
60–69	4	1.04

In Table 2 we have divided the arthritic patients into decades, and it appears that the older age groups had more abnormal initial biophotometer readings. However, when the dark-adaptation values of arthritic patients between the ages of twenty and twenty-nine are compared with those of controls of the same age decade, they are seen to be definitely abnormal (Table 3).

The 30 per cent of the patients who were moderately or severely deficient showed no obvious clinical manifestations of vitamin A deficiency, that is, xerophthalmia or keratomalacia. Hemeralopia (night blindness) was subjectively noticed by only 1 of the patients. During the test, several complained of nyctalopia, the condition of being more easily dazzled by light than normally.

The amount of supplemental vitamin A required to give and maintain initial biophotometer readings of 0.50 millifoot candles or less in the 13 patients in Group B is shown in Table 4. Seven of this group were on the regular hospital diet throughout the experiment; the rest spent part of the time at home. It will be noted that the supplementary doses of vitamin A sufficient to maintain normal readings in these patients ranged from 25,500 to 68,000 U.S.P. units daily.

To illustrate the usual effect of vitamin A therapy the protocol of Case 12 is produced in Figure 2. In addition, it can be seen that while the patient was on a satisfactory maintenance dose of vitamin A (51,000 U.S.P. units) there was an exacerbation of arthritic symptoms, with an increase of the erythrocytic sedimentation index and of the initial biophotometer reading.

In a few patients who were in the quiescent stage of the disease, tests were made after the withdrawal of vitamin therapy and a marked fall in the dark-adaptation curve was observed.

Fifteen arthritic patients with erythrocytic sedimentation indices between 0.67 and 1.33 mm. per minute demonstrated no apparent relation between this index and the initial biophotometer reading.

TABLE 3. *Relation of Dark-Adaptation Curves to Age of Controls and of Rheumatoid Arthritic Patients.*

Group	No. of Cases	Age Range	Average Biophotometer Readings				
			Initial	2½ min.	5 min.	7½ min.	10 min.
		yr.	*mft. cand.*	*mft. cand.*	*mft. cand.*	*mft. cand.*	*mft. cand.*
Controls	11	20–29	0.32	0.07	0.03	0.03	0.02
Rheumatoid arthritic patients	21	20–29	0.63	0.16	0.08	0.05	0.03

However, in all but 3 of 20 patients with indices greater than 1.33 mm. the reading ranged from borderline to a severe deficiency. All of 10 patients with indices less than 0.66 mm. had normal initial biophotometer readings. The erythrocytic sedimentation index has been considered the most satisfactory laboratory test aiding in the recognition and evaluation of patients with rheumatoid arthritis,[19] and it appears that this index roughly parallels the initial biophotometer readings in these same patients.

TABLE 4. *Rheumatoid Arthritic Patients (Group B) Receiving Supplemental Vitamin A.*

Case No.	Age	Sex	Duration of Disease	Erythrocyte Sedimentation Index Range	Initial Biophotometer Readings		Duration of Vitamin A Therapy	Type of Diet	Final Daily Supplementary Dose of Vitamin A
					before vitamin A	after vitamin A			
	yr.		*yr.*	*mm./min.*	*mft. cand.*	*mft. cand.*	*wk.*		*U.S.P. units*
1	23	M	1	1.00–1.70	0.80	0.18	13	Ward	25,500
2	45	F	1	1.05–1.15	0.69	0.44	7	Ward	25,500
3	15	F	1	1.50–2.00	1.08	0.44	14	Ward	34,000
4	29	M	6	0.87–1.10	1.00	0.29	9	Home	34,000
5	47	F	9	0.74–0.98	0.84	0.31	8	Home	34,000
6	41	F	20	1.10–1.80	1.00	0.44	6	Home	42,500
7	48	F	9	0.70–1.00	1.10	0.38	8	Home	42,500
8	32	F	6	0.70–1.05	1.60	0.44	10	Home	51,000
9	43	F	11	1.00–1.85	1.00	0.47	12	Home	51,000
10	27	M	10	0.45–1.50	1.60	0.47	11	Ward	51,000
11	49	M	17	1.50–2.00	0.84	0.44	12	Ward	51,000
12	55	F	1	1.50–2.00	1.50	0.47	17	Ward	59,500
13	54	F	18	0.80–1.65	1.80	0.44	15	Ward	68,000

Discussion

Booher[20] quotes the Technical Commission on Nutrition[21] as recommending 2000 to 4000 units of vitamin A as the daily requirement for normal adults. The average well-rounded diet contains about 6000 units of vitamin A and is therefore sufficient to maintain normal dark adaptation.[22] Jeghers[22] and others[14, 23, 24] have observed that a vitamin-A-deficient but otherwise healthy individual returns to normal in two or three weeks on an intake of 10,000 U.S.P. units of vitamin A per day. The presence of high fever,[25] chronic infection[26, 27] or cirrhosis of the liver[28] has been shown to diminish the amount of vitamin A or its function in the body.

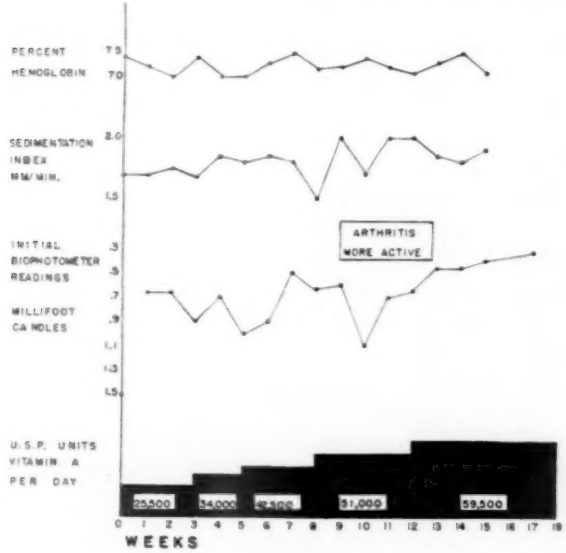

FIGURE 2.

The chart gives the data on a woman (Case 12), aged fifty-five, with fusiform polyarthritis in all joints of one year's duration. The roentgenographic diagnosis was rheumatoid arthritis.

We have shown in this paper that in rheumatoid arthritis, as in other chronic or infectious diseases, there is an increased demand for vitamin A, as measured by the dark-adaptation curve. Also, many arthritic patients require from four to ten times the amount of vitamin A present in their regular diet to maintain normal dark-adaptation curves.

There is no means of determining at present whether in these patients this increased need represents an increased utilization, decreased absorption or an inactivation of the vitamin. Until more is known of the mechanism of vitamin A metabolism, the normal intake of vitamin A in the patient with rheumatoid arthritis can be measured by the method at hand.

The provision of adequate vitamin A therapy for our patients effected no clinically observable favorable result, but it would be most desirable to eliminate an existing deficiency of this vitamin as a general supportive measure in rheumatoid arthritis.

Summary

Patients with rheumatoid arthritis showed much higher average dark-adaptation curves than did a group of controls, as measured by the biophotometer. This was found to be true even after age corrections had been introduced.

Sixty-five per cent of a group of 79 rheumatoid arthritics showed abnormal dark-adaptation curves. These high readings may be interpreted as an indication of borderline to severe vitamin A deficiency.

Supplemental doses of from 25,500 to 68,000

U.S.P. units of vitamin A per day were necessary to establish and maintain normal levels.

In 45 cases tested the degree of vitamin A deficiency roughly paralleled the severity of the disease, as indicated by the erythrocytic sedimentation index.

In patients receiving adequate vitamin A therapy no obvious clinical improvement was noted that could be attributed to the effect of the vitamin.

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CARCINOMA OF THE AMPULLA OF VATER*

Report of a Three-Year Cure

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CARCINOMA of the ampulla of Vater is a relatively rare clinical entity. The picture is that of obstruction of the bile and pancreatic ducts.[1] The diagnosis usually made is carcinoma of the head of the pancreas. Although the tumor appears histologically to be of a low grade of malignancy, the expectation of life is very short. Outerbridge[2] reports an average survival of seven and a half months in a series of 47 cases. Regional and distal metastases are late, probably because death occurs so early.[3] Symptoms occur early because of obstruction of the bile and pancreatic ducts. Speaking of carcinoma of the ampulla of Vater, Upcott[4] remarks, "There is probably no position within the body outside of the central nervous system where a growth, while yet so small, is heralded by more widespread symptoms."

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Early discussions of carcinoma of the ampulla of Vater are those of Halsted[5] in 1900 and Outerbridge in 1913, the latter having collected 110 cases. Recent complete studies include those of Cohen and Colp,[3] Hunt and Budd,[6] Cooper[7] and Lieber, Stewart and Lund.[8]

INCIDENCE

At the Jefferson Hospital, Philadelphia, there were 4 cases in 4154 autopsies, an incidence of 0.09 per cent.[8] Kellogg[9] reports 50 cases in more than 151,000 autopsies, an incidence of 0.03 per cent. Lieber, Stewart and Lund found an incidence of 0.06 per cent, 14 cases occurring among 22,152 autopsies. Various authors note that ampullar carcinoma is the commonest form of carcinoma of the duodenum. Hoffman and Pack[10] report that of 228 cases of cancer of the small bowel, 104 (46 per cent) were in the duodenum, and that of these duodenal tumors 62 per cent were at the ampulla of Vater.

Age Distribution

The majority of patients are over forty years of age. The average age in Outerbridge's series was fifty-four, in Cooper's forty-nine. However, patients as young as fifteen, sixteen and eighteen have been reported in the series of Lieber, Stewart and Lund, and Mayo-Robson[11] reports the case of a patient aged thirty years.

Sex Distribution

The disease is commoner in men than in women. In the large series of Lieber, Stewart and Lund there were 139 males and 83 females, a ratio of 5:3.

Etiology

Several etiologic factors are mentioned but nothing definite is known concerning them, since evaluation is difficult. Chronic irritation is undoubtedly present, resulting from a constant interplay of acid gastric juice and alkaline pancreatic juice.[3]

Cholelithiasis occurs in 12 to 22 per cent of cases of different series. Gallstones occurred in 20 per cent of Outerbridge's 110 cases, and 22 per cent of Cooper's 14 cases. Lieber, Stewart and Lund report an average of 16 per cent. These figures are above the normal expectation, as only 8.8 per cent of 22,152 autopsies at the Philadelphia General Hospital revealed gallstones.[8]

Clinical Considerations

As already noted, the patient is usually in the cancer age. The symptoms and signs are those of obstruction of the common bile and pancreatic ducts, in addition to duodenal ulceration (Table 1). There is usually a history of painless, afebrile, fairly constant jaundice, insidious in onset. However, more or less painful jaundice occurs in almost 50 per cent of cases. There may be weight loss, anorexia, vomiting, diarrhea or epigastric distress. McCabe[12] has suggested that in later stages, when the tumor growth becomes large, pain may result from hypermotility of the duodenum. Physical examination reveals jaundice, emaciation and a distended gall bladder, unless previous gall-bladder disease has caused fibrosis and contraction of the gall-bladder wall. Epigastric pain may be related to the finding of cholelithiasis. The liver edge is usually palpable. The usual diagnosis is carcinoma of the pancreas. A diagnosis of carcinoma of the ampulla of Vater can be made definitely only at operation or autopsy.

Table 1. *Frequency of Symptoms and Signs Based on the Figures of Cooper[7] and of Lieber, Stewart and Lund.[8]*

Symptom or Sign	Cooper	Lieber et al.
	%	%
Jaundice	95	98
Abdominal pain	86	59
Weight loss	78	
Anorexia	71	
Vomiting	36	58
Diarrhea	21	
Palpable gall bladder	50	50
Enlarged liver	86	78
Occult blood in stool	82	
Duodenal defect in gastrointestinal series	80	32

Treatment

Since this tumor is usually small, produces early symptoms, metastasizes relatively late and, if untouched, kills early, surgery is justifiable. Operability is frequent, but surgical technical difficulties are great. The operative mortality rates vary from 30 to 70 per cent, with a tendency to approach the lower figure in recent years. Hunt and Budd note that the mortality rate of palliative procedures with various biliary anastomoses still approaches 70 per cent, whereas radical extirpation of the tumor with direct implantation of the bile and pancreatic ducts into the duodenum yields a mortality of about 40 per cent. Cohen and Colp report a series of radical extirpation of the tumor with a 43 per cent operative mortality.

Lieber, Stewart and Lund state that the operative mortality with a palliative procedure is 78 per cent (51 cases), and with primary resection of the tumor 30 per cent (57 cases).

Recurrence after radical extirpation of cancer of the ampulla has been frequent. Many patients live less than one year, the average duration of life being two years after the onset of symptoms.

Cures are infrequent. Muller and Rademaker[13] list 7 patients surviving transduodenal resection of ampullar carcinoma after four years. Hunt and Budd add an eighth case. The case reported in this paper is that of a three-year cure, the patient being symptom-free to the date of writing.

The procedures of choice are transduodenal resection with reimplantation of bile and pancreatic ducts, and Whipple's two-stage procedure. As Cooper notes:

> It is obvious that no single radical procedure is suited to all variations of the disease. If the tumor is small, papillary, free of ulceration and more or less pedunculated without infiltration at its base, transduodenal resection with reimplantation of the ducts should be the ultimate procedure. If the tumor is ulcerating and infiltrates the duodenal wall, transduodenal resection obviously is not the procedure of choice from the viewpoint of permanent cure.

In these cases Whipple[14, 15] advises a two-stage procedure. The first stage includes posterior gastroenterostomy, ligation and section of the common duct below the cystic duct after determining the patency of the cystic duct, leaving a long,

slack silk ligature as an indicator on the lower stump of the sectioned common duct, and cholecystojejunostomy. Three or four weeks later the second stage is undertaken, as follows: ligation of the pancreaticoduodenal and gastroduodenal arteries; resection of the descending portion of the duodenum with inversion of the upper and lower ends, and a V-shaped excision of the head of the pancreas and common duct; ligation of the cut ends of the pancreatic ducts and suturing of the two cut surfaces of the pancreas with interrupted fine-silk sutures, and the placing of a cigarette drain in the bed of the resected duodenum.[7] Whipple emphasizes that the mortality is greater with one-stage procedures than with two-stage, that local removal of the growth results in a higher mortality, and that local excision of the ampulla through the duodenum with reimplantation of the common bile duct carries the danger of peritonitis and duodenal fistula.

However, statistics of operative mortality are of relative value only, since a great number of palliative procedures are performed on poor surgical risks. Thus in different series cholecystotomy often has a higher mortality rate than has cholecystectomy, since the former is usually performed only on very ill patients. As Lieber, Stewart and Lund state:

> The degree of surgery employed in any individual case must depend upon the general condition of the patient, the character and extent of the primary lesion, the presence of extension or metastases and the degree of biliary, pancreatic or duodenal obstruction.

Preoperative preparation includes a high-carbohydrate diet, adequate fluid intake (3000 to 3500 cc. daily), infusions of glucose when necessary and blood studies embracing blood-cell counts and the determination of bleeding and clotting times and prothrombin level. Quick's[16] method or modifications thereof may be used to determine the blood prothrombin level. It is wise to feed vitamin K and bile salts regardless of this level, since it is now known that a marked fall in the prothrombin concentration may occur postoperatively. If the level is normal, vitamin K and bile salts are given in the form of 1 Klotogen and 2 Bilein capsules, three times daily. If the prothrombin level is below 80 per cent of normal, larger doses are given (2 Klotogen and 3 Bilein capsules, three times daily) until the prothrombin concentration reaches at least 80 per cent.

Postoperatively vitamin K and bile salts are resumed. Glucose infusions in physiologic saline are given. Since the daily salt requirement averages from 3 to 10 gm. per day, only the first 1500-cc. infusion is given in physiologic saline, the remaining 1500 to 2500 cc. of fluid consisting of 5 per cent glucose in distilled water. Tight abdominal binders are avoided. Transfusions are given as indicated.

Case Report

L. F. V. (No. 45943), a 76-year-old woman, was referred by Dr. W. Richard Ohler and admitted to the Faulkner Hospital on October 27, 1936. For the previous 2 months she had noted anorexia, occasional nausea without vomiting and a tendency to constipation. She thought she had lost weight, but was not sure of the amount. Slight jaundice appeared 2 weeks before admission.

The temperature on admission was 98° F., the pulse 80, and the respirations 20. The blood pressure was 155/80. Physical examination revealed a patient in no acute distress but with icteric skin and scleras. The head, neck, heart and lungs were normal. The liver, gall bladder, spleen and kidneys were not palpable. There were no abdominal masses, tenderness or shifting dullness. The urine had a specific gravity of 1.022; it contained the slightest possible trace of albumin and no sugar, and was negative for bile by the foam test. The urinary sediment was negative. The red-cell count was 4,300,000, with a hemoglobin of 84 per cent (Sahli). The white-cell count was 8300, with a normal differential count. The icteric index was 25. The blood nonprotein nitrogen was 30 mg. per 100 cc., and the blood sugar 100 mg. A blood Hinton test was negative. Stools were negative for occult blood by the benzidine test on one occasion, and ++ by a guaiac test on a second. An oral Graham test showed no filling of the gall bladder with the dye either before or after the fat meal, and there was no evidence of stone. A gastrointestinal series revealed a normal esophagus, stomach and duodenum, with no gastric retention.

The preoperative diagnosis was carcinoma of the pancreas. Operation was performed by one of us (E. L. Y.) on November 17, 1936. The abdomen was opened, using a right-rectus incision. The gall bladder was found to be considerably enlarged, thin-walled and without stones, but there were no adhesions. The gall bladder was opened, and a suction tube inserted, with the removal of much thick, ropy bile. The liver was normal to inspection and palpation. The pancreas was soft and normal, except for a small nodule at the head, in the region of the lower end of the common bile duct. The latter was opened. A transverse incision was made into the duodenum, and a tumor of the papilla was found. The nodule was excised, apparently completely. The common bile duct and pancreatic duct were identified, sutured together and then sutured to the wall of the duodenum. The duodenum was closed in two layers. A T tube was placed in the common bile duct. The wound was closed in layers, with a cigarette wick.

The pathological report, by Dr. J. Beach Hazard, was as follows:

> Gross examination shows a roughly oval mass 1.5 by 1.0 by 0.6 cm. The mucosal surface presents centrally a bulging area, 0.6 cm. in diameter and about 0.3 cm. in height, which is gray to pinkish-gray, granular and of hard consistence. Centrally there is a slit-like depression, and through this a probe can be passed from the mucosal surface. Surrounding this opening is a narrow margin of soft, gray tissue measuring from 1.0 to 0.3 mm. wide. All other surfaces are surfaces of excision and are thus somewhat irregular. The marginal tissue, however, is of soft consistence.

Microscopical examination shows the epithelium of the papilla to be replaced for about two thirds of its extent by atypical epithelial cells forming rather large irregular lumens (Fig. 1). Almost the entire duct lining in the section taken is formed by cells of this character. They are roughly columnar, and many times form several layers. They extend into the duct wall for a distance of about 3 mm. Only a few mitoses are found. Tumor is present at the line of excision.

FIGURE 1. *Section through the Papilla of Vater, Showing Replacement of the Normal Mucosa by Atypical Epithelium (× 50).*

Diagnosis: malignant adenoma (adenocarcinoma), growing fairly slowly.

The convalescence was satisfactory but long. There was no distention, sepsis or hemorrhage. Jaundice diminished rapidly. Nausea, vomiting and constipation were the primary postoperative complaints. The intravenous administration of 5 per cent glucose in saline solution was utilized to maintain the fluid and ion balance. In order to rule out intestinal obstruction, on the 16th postoperative day a small amount of barium was given by mouth. This revealed evidence of slight delay through the duodenum but no actual obstruction. Nausea and vomiting became less frequent, and finally ceased, and the patient was discharged on the 25th postoperative day. Annual follow-up studies have revealed an apparent cure, the patient being symptom-free up to December, 1939.

SUMMARY

Carcinoma of the ampulla of Vater is a relatively rare disease, with a clinical picture of obstruction of the bile and pancreatic ducts.

Incidence based on autopsy statistics is about 0.04 per cent of all necropsies.

Most patients are over forty years of age, and the disease is commoner in men than in women (5:3).

The etiologic factors are unproved, but possible factors are chronic irritation and cholelithiasis.

The important clinical findings are jaundice, abdominal pain, weight loss, anorexia, palpable gall bladder and liver, and occult blood in the stool.

The proper treatment is an early operation whenever the diagnosis is suspected and there are no evident metastases. The procedures of choice are transduodenal excision of the tumor with reimplantation of the common bile and pancreatic ducts, and the two-stage Whipple operation. Operative mortality is high but if untreated the tumor inevitably causes death. At the present time, with the higher mortality of the Whipple procedure, and the lack of any cures, transduodenal resection of the duodenum with reimplantation of the common bile and pancreatic ducts appears to be the procedure of choice with small, completely resectable growths. For the large tumors, however, the Whipple operation should be employed.

The case reported is one of proved ampullar carcinoma, treated by transduodenal resection with reimplantation of the common bile and pancreatic ducts. The patient is alive and symptom-free in the fourth year after operation.

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REPORT ON MEDICAL PROGRESS

BACTERIOLOGY

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SULFANILAMIDE THERAPY

ALTHOUGH the introduction of sulfanilamide still remains the most important development for the clinician in the field of infectious disease, little space will be devoted to chemotherapy here, because so much has been written on the subject elsewhere. For the further development of this field it is most important to learn how these drugs act. Two different sets of observations have thrown some light on this problem. First, substances have been isolated from bacteria and tissues which both stimulate bacterial growth and inhibit the action of sulfanilamide.[1-3] *P*-aminobenzoic acid is one such inhibitor that has been identified, and its presence in pus may be the reason why sulfanilamide is so ineffective in abscesses.[4, 5] Presumably, sulfanilamide acts because it is used as an ineffective substitute for the inhibitor by strains that are unable to synthesize *p*-amino-benzoic acid in sufficient amounts when it is absent from the medium. Secondly, oxidation products of sulfanilamide have been found in the blood[6] and urine[7] of treated patients, and in growing cultures[8] that contain sulfanilamide. These products are themselves strong oxidizing agents, producing methemoglobinemia and cyanosis in the patient,[6] and it is postulated that they inactivate certain bacterial enzymes that are highly sensitive to oxidation.[8, 9] There is not as yet enough evidence at hand to reconcile these two lines of investigation.

SYPHILIS

In these days no review would be complete without a reference to syphilis, and three reports deserve mention. Turner[10] has been able to demonstrate definite protective antibodies in the serum of infected rabbits. Mixtures of their serum with syphilitic material injected into the skin of rabbits produced smaller lesions than did mixtures of normal serum with the same material. Eagle[11] has shown that syphilitic blood contains spirochetal antibodies and that absorption with spirochetes will remove both spirochetal and Wassermann antibodies, whereas absorption with the tissue antigen used in the Wassermann reaction removes only its own antibodies, leaving the former intact. This suggests that the Wassermann reaction is due to an antibody that is called forth by an antigen present in the spirochetes themselves, and not by some product of tissue damage. The most interesting development in the therapeutic field has been the massive-dose method which is being tested by a group[12] at Mt. Sinai Hospital, New York City. Patients with primary and secondary syphilis are given a continuous intravenous infusion containing an arsenical drug twelve hours a day for five days, and no more treatment thereafter. The results indicate that this is a reasonably safe procedure and quite an effective one. Though the method is not recommended for general use, it has great possibilities if time shows that such cures are lasting.

INFLUENZA

A great deal of work is being done on influenza in this country and England. Typical swine influenza is caused by combined infection with a filterable virus and the influenza bacillus,[13] but human influenza is caused by the virus alone,[14] although its worst complications and mortality were due to secondary bacterial invaders in the great pandemic of 1919. Immunity can be produced by an intracutaneous or subcutaneous injection of live virus.[15] This is harmless to the individual, but when tried in swine started several epidemics due to the discharge of virus from the nose.[16] The duration of immunity is relatively short. Various forms of inactivated virus seem capable of inducing immunity in laboratory animals,[17, 18] but until the immunological relation between various strains of virus is worked out for human beings, prophylactic vaccination on a large scale will not be feasible. It is quite possible that none of the present strains of virus would protect against a strain causing a new pandemic.[19]

UNDULANT FEVER

Undulant fever is a disease that is much talked about but not very often seen in Massachusetts. Recent investigations in areas where brucella infection is prevalent have shown that chronic bru-

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cellosis is far commoner[20–22] than the typical acute disease. The symptoms of this form of infection may be so vague that the patients are considered neurasthenic, and in some cases all the usual laboratory tests are negative.[23] Through the efforts of Huddleson,[24] Poston[25] and others,[26] these tests are being constantly improved, but for the practitioner all that is available at present is the agglutination test, blood culture and finally a skin test with a 1:5 dilution of a commercial vaccine. In the agglutination test and skin test the bovine variety of *Brucella abortus* is generally used because it is commoner than the caprine or porcine variety, but actually any one of the three varieties may be used because of the close antigenic relations in this group. A great deal of work will be necessary before we can evaluate the proper significance of these tests in relation to vague symptoms of ill-health in a given individual. Certainly no one would suggest that flat feet were due to tuberculosis merely because the patient happened to have a positive tuberculin test, and like tuberculosis, brucellosis has been shown to be remarkably widespread in this country, both in man and in domestic animals.[20, 23]

Gonorrhea

Gonorrhea has begun to receive the attention it deserves as one of mankind's commonest afflictions. The improved methods of culture for this fastidious micro-organism have made its isolation relatively simple. Essentially, successful cultivation depends on a medium rich in proteins, adequate moisture, slightly increased carbon dioxide tension and careful temperature regulation. A dehydrated chocolate agar is now on the market which fulfills the first two conditions when fresh. Incubation of the plates in a sealed candle jar, as originally proposed by Nye and Lamb,[27] guarantees sufficient moisture and carbon dioxide. A few strains will grow only at a temperature of 34°C., a few others at 37°C. only, but for routine work 35 to 36°C. has been found satisfactory. McLeod and his associates[28] introduced the use of a dye, dimethyl-para-phenylene diamine, which is allowed to run across part of the plate after it has been incubated for forty-eight hours. This imparts a pink color to the gonococcal colonies because of the action of an oxydase that they possess,[29] and makes it possible to pick up a few colonies in mixed cultures which otherwise might have been missed. This is particularly valuable in cultures from the uterine cervix. Since the dye test is not absolutely specific, colonies thus identified must be fished and sugars inoculated for final identification. Pitts[30] has recently published another method, which may ultimately prove even better. The importance of good cultural methods is shown by Leahy and Carpenter's[29] figures to the effect that his cultural method, used in conjunction with smears, was 10 per cent more effective than smears alone in detecting cases. Negative cultures have now become one of the most valuable criteria of cure in difficult cases.

The first real advance in the therapy of gonococcal infections came with the study of the thermal death times of strains by Carpenter et al.[31] They found that most strains, particularly those freshly isolated, were very susceptible to heat, and were killed in less than five hours at a temperature of 106.7°F. (41.5°C.). This put fever therapy on a rational basis, and the Rochester group, like many others, have secured excellent results in the treatment of resistant cases with artificial fever.[32] In most cases one treatment of five hours at a temperature between 106 and 107°F. is sufficient to effect a complete cure. Treatment must be in the hands of an expert, as it is a rigorous procedure and demands knowledge, judgment and technical skill for its safe administration.

For the ordinary case, chemotherapy remains the method of choice. A few points seem to stand out from the mass of literature on this subject. First, it is best to wait at least a week after onset before administering the drug; secondly, chemotherapy should produce a marked improvement within several days if dosage is adequate and if the drug is going to be effective; and thirdly, very rigid criteria must be fulfilled after the cessation of treatment if the case is to be considered cured. It has been shown by Westphal, Charles and Carpenter[33] that gonococci may be made resistant to sulfanilamide or sulfapyridine in vitro by growing the organisms in gradually increasing concentrations of the drug.

Poliomyelitis

It has long been assumed that poliomyelitis is spread by droplet infection, since the only method besides intracerebral inoculation by which monkeys may be regularly infected is the intranasal instillation of virus. Some students of the disease have always opposed this view because epidemics usually occur in late summer and tend to disappear with the first cold weather, like so many insect-borne diseases and enteric infections.

During the past year several investigators[34–36] have successfully demonstrated poliomyelitis virus in the stools of patients and convalescents, and others[37] have shown that it may persist for as long as one hundred and twenty-three days after the illness. In one epidemic several healthy contacts were

also examined and found to excrete the virus in their feces.[35] The fact that the virus was found oftenest in the stools of young children suggests that its presence may have been due to the swallowing of secretions from the nasopharynx. Trask and Paul,[38] however, believe that it is easier to isolate poliomyelitis virus from the stools than from nasal washings, but this may be due to the method employed. The stool itself represents a natural concentrate of a twenty-four hour specimen of waste products, and in preparing material for monkey inoculation to test the virus a stool specimen is extracted, the extract concentrated and a large volume injected. This work does not rule out the nasopharynx as the primary source of the virus, but it does show that virus is able to survive in the feces and may be excreted by this route for a very long period of time even after an inapparent infection. Furthermore, Trask and his associates[39] detected poliomyelitis virus in the sewage of two out of three cities with active epidemics in progress; they could obtain it in effluents a half mile below isolation hospitals in which poliomyelitis patients were being treated. This is a striking confirmation of what has long been known in the laboratory; namely that the virus of poliomyelitis is remarkably stable and resistant to chemical manipulations.

As part of this work, Trask, Paul and Vignec[40] attempted to demonstrate the virus in so-called "abortive" cases. Paul, Salinger and Trask[41] had shown that in households where cases of frank poliomyelitis occurred, a number of mild illnesses characterized by malaise, fever, headache, coryza, sore throat, vomiting or diarrhea almost invariably occurred among the other children. From 3 such cases suspected of being nonparalytic poliomyelitis they[40] were able to isolate virus, in 1 case from the nasopharynx and in 2 cases from the stools. This gives more definite proof to the belief that neutralizing antibodies in the serum of most adults are due to very mild infections in childhood, and that paralysis is the exception rather than the rule in this disease. The work of Aycock,[42] who is attempting to show that susceptibility to paralytic poliomyelitis is a hereditary characteristic associated wth a certain type of body build and endocrine constitution, is interesting in this connection.

Another question of great interest is whether the virus in human epidemics must enter the nasopharynx or may be transmitted by the bites of insects. Most of our knowledge of poliomyelitis is based on experimental work with laboratory strains that have been passed from monkey to monkey by intracerebral or intranasal inoculation. Many viruses have become fixed by artificial laboratory manipulation, and thus acquire new and different characteristics when tested in their original host. Trask and Paul[43] attacked this problem and found that recently isolated strains of poliomyelitis virus were often capable of producing infection in monkeys by intracutaneous injection, although the old laboratory strains were strictly neurotropic.

One of the greatest obstacles to large-scale research in this disease has been the fact that man and monkeys are the only susceptible animals. Armstrong[44] recently succeeded in establishing the Lansing strain of virus in the Eastern cotton rat, and he[45] was then able to transfer the disease from these rats to white mice, in which it produced nonfatal paralyses in a large proportion of inoculated animals. Pathologically, the lesions resemble those in monkeys and man, and the virus has retained its virulence for monkeys.[46, 47] Unfortunately, this procedure has so far been possible only with this one strain of virus, and many other strains have failed to infect the cotton rat.[48]

In summary, poliomyelitis is a disease which produces many abortive cases and few paralytic ones, and thus most of the population become immune. The virus may be obtained from the nasopharynx and the stools of the abortive cases for several weeks, and may even be detected in sewage contaminated with their feces. The implications of this are clear. Cases of poliomyelitis and any cases of mild vague illness among contacts should be strictly isolated, with the precautions used in the care of both respiratory and enteric diseases. We still do not know how the disease actually spreads, but these facts give some credence to the old idea that poliomyelitis tends to be associated with bathing places, especially rivers and swimming pools. Ellsworth[49] has written an extremely interesting presentation of this point of view.

Viruses and Immunity in Tumors

Investigations in cancer have followed so many lines that almost every fundamental science can claim the tumor problem as its own. Bacteriology and immunology have a claim which was first staked out by Jensen[50] when he found that mice in which sarcomas failed to grow became resistant to further attempts at tumor implantation. In recent years interest has again been focused on this finding, and the general principle confirmed that in animals with malignant tumors there develops some form of resistance to further attempts to implant that particular tumor in the animal. Andervont[51] showed that if mouse sarcoma was induced in the tails of mice, and

the tails were amputated after several weeks, the animals remained resistant to implantations of this tumor elsewhere. With the Brown-Pearce carcinoma of rabbits, Besredka[52] showed that the injection of tumor cells into the skin induced the formation of tumor nodules which regressed and disappeared after a variable time. When they regressed, the animals became immune to intratesticular inoculation, although this led to the induction of rapidly growing, metastasizing carcinomas in most normal rabbits. This means that the growth of tumor at one site induces a changed reactivity, that is, immunity, to the tumor cells in any other part of the body. Thus, the tumor must either give rise to antigenic material which is absorbed and which produces a general immunity, or else must induce a local production of antibodies which protect the rest of the organism. In order to be antigenic, a tumor must differ chemically in some way from the normal body tissues. It has been suggested that tumor cells themselves differ in their chemical make-up, and support was lent to this theory by Kögl,[53] who apparently found a high percentage of dextro-rotatory glutamic acid in malignant cells, while normal cells contained only laevo-rotatory glutamic acid. However, this work has not yet been confirmed.

Another theory is that these tumors contain a virus which is the antigenic substance. Virus tumors have been known for a long time, and include many common diseases, such as warts in human beings, Rous chicken sarcoma, fowl leukemia and the Shope papilloma and infectious myxomatosis of rabbits. In these diseases the tumor can be transmitted by the injection of a filtrate of ground tumor tissue. When the Shope papilloma virus was discovered in the wild rabbits of the Middle West it was soon noted that virus could usually be found in the papillomas. However, if domestic rabbits were inoculated and developed papillomatosis, the tumors were much less differentiated than those in wild rabbits, frequently becoming malignant, and the virus could never be isolated from them (Kidd[54]). It was evident that virus was present because the rabbits developed neutralizing and complement-fixing antibodies for the virus. It has since been found that when wild rabbits develop malignant changes in the papillomas, as they occasionally do, the virus can no longer be demonstrated in the tumors.[55] Kidd came to the conclusion that the virus was masked in these tumors because the disorderly growth led to extravasation of blood into the tumor, and this blood carried sufficient antibody into the tissues to neutralize the virus. In the orderly papillomas of wild rabbits this extravasation did not occur and there was less absorption of virus into the circulation, and therefore less antibody was present.

With this work in mind, Kidd[54] reinvestigated the Brown-Pearce carcinoma. This very malignant tumor more nearly resembles human carcinoma than any other experimental tumor. It is transmissible only by living cells; it takes with regularity only in the testicle; it metastasizes to the regional lymphatics and thence to the internal organs. It arose spontaneously in a syphilitic rabbit seventeen years ago and has been kept going ever since by rabbit passage.[56] By the same technic he used in the papilloma work, Kidd[57] showed that a saline extract of the fresh tumor tissue contained a substance of high molecular weight, which was similar to the substance obtained from the papillomas and presumably identical with the virus. It was entirely comparable immunologically, since it fixed complement specifically with the serums of rabbits harboring this tumor and no other. However, it differed in that it failed to produce the tumor when injected into the testes of susceptible rabbits. Cheever[58] has confirmed these complement-fixation experiments, although his incidence of positive reactions was considerably lower. This work is of great theoretical importance because it represents the first step toward bridging the gap between carcinoma as we see it in man and the virus tumors of animals.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26291

PRESENTATION OF CASE

A forty-two-year-old American store clerk was admitted to the hospital complaining of a nonproductive cough.

Two years before admission, following a severe cold, the patient developed a nonproductive, brassy cough, which persisted without change until the time of his admission to this hospital. The cough was on occasions made worse by smoking and was occasionally productive, especially in the morning, of small amounts of greenish sputum, which was never blood-tinged or malodorous. He noticed no night sweats, orthopnea, dyspnea or hemoptyses. Save for the cough, he was well until one month before admission, when he developed another cold and for several days experienced substernal pain, which was relieved by standing or lying on his side and aggravated by lying on his back. He consulted a physician, and roentgenographic examination of the chest showed a mass in the lower mediastinum. The mass was described as being "grapefruit in size" and was located "near the midline"; the lungs were "clear." He was treated in an outside hospital by a series of three x-ray treatments over the mass, but it was stated that it had not decreased in size after a period of several weeks. He was then referred to this hospital for further diagnosis and treatment.

Six years before admission, he had suffered an attack of "mild pleurisy" in the left chest, accompanying a cold. His weight had always been constant, and his general health good. The remaining family, marital and past histories were non-contributory.

Physical examination revealed a slightly obese man who appeared well. He had an occasional brassy cough. The heart was slightly enlarged, with the apex impulse seen and felt 10 cm. to the left of the sternum, or 2 cm. beyond the midclavicular line in the fifth interspace. The heart sounds were loud and slapping, especially the pulmonic second sound, which was greater than the aortic second sound. The blood pressure was 190 systolic, 120 diastolic. Examination of the lungs showed a patch of increased vocal fremitus, with normal breath sounds and no rales, over the left lower chest posteriorly in the vicinity of the angle of the scapula. The remainder of the physical examination was negative.

The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 5,000,000 with 16.9 gm. of hemoglobin (photoelectric-cell technic), and a white-cell count of 17,200 with 79 per cent polymorphonuclears; a smear was normal. Examination of the urine was negative. No acid-fast bacilli were found in the sputum. The serum protein was 6.5 gm. per 100 cc., the blood nonprotein nitrogen 26 mg. A sputum culture showed a moderate number of beta hemolytic streptococci.

Roentgenograms of the chest showed a round mass measuring approximately 10 cm. in diameter in the posterior mediastinum, the center of the mass being opposite the seventh dorsal vertebra. It showed transmitted pulsation. The mass lay slightly more to the left than to the right side and showed no evidence of calcification. Examination, including films in the horizontal and upright positions, showed no definite change in the shape of the mass by gravity. It moved markedly upward during the swallowing act. The esophagus was in intimate contact with the mass, running along its posterior surface, slightly to the right. The esophagus in this area was markedly flattened, being narrow in the anteroposterior direction and wide in the transverse direction. In the profile view the top of the lesion produced a very abrupt change in the course of the esophagus. A definite edge was, however, not visible in the end-on view of the organ. The carina was spread apart by the mass, and the left main bronchus was markedly narrowed. There was a triangular area of marked homogeneous density along the left lower thoracic spine, which extended upward toward the region of the hilus. The heart was slightly displaced to the left but showed no unusual respiratory shift. The lung markings on the left side were slightly less than those on the right. There were a few linear areas of decreased density in the left lower-lung field, probably representing localized areas of atelectasis.

On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MERRILL SOSMAN:* This indoor sport of differential diagnosis reminds me very much of riding after the fox with a pack of hounds. I

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shall be the leader of the hunt and you will be the pack of hounds. Please bay when you see the quarry.

It is impressive to me how often an ordinary cold seems to precipitate symptoms that are in no way related to the cold, just as in this case. It simply gives something for the patient to date the onset of his symptoms.

"Save for the cough he was well. . . ." That quite well rules out tuberculosis, chronic pulmonary suppuration, carcinoma of the lung and metastatic cancer.

The only thing that clicks in my memory in relation to the statement regarding substernal pain relieved by standing or lying on his side is a hiatus hernia, with a large portion of the fundus of the stomach herniating through the esophageal hiatus. A patient with such a hernia may get relief from discomfort or pain by standing up or lying on the side. It is purely a mechanical effect due to the release of the pressure.

I have no idea how much x-ray therapy was given since the total roentgen units are not specified. Ordinarily 250 to 300 r are given in a single treatment. So he presumably had 750 to 900 r. That is plenty to cause a definite decrease in malignant lymphoma, so we can assume for the time being that this was not malignant lymphoma.

"Physical examination revealed a slightly obese man who appeared well." Obviously he did not have cancer, and no serious involvement, such as tuberculosis or chronic pulmonary suppuration.

I compliment the abstracter for leaving out the percussion measurements of the heart. They are very inaccurate and unreliable; and, as Dr. Cabot, who originated these exercises, preached fifteen years ago, the visible apex impulse or the location of the apex by palpation is of a great deal more value than the evanescent dullness of percussion.

I do not know what "slapping" heart sounds mean. They may mean that the heart was pushed against the chest wall more than usual and that there was much more of a snap to systole than ordinarily.

The blood pressure reading indicates moderate hypertension in a man of forty-two; it was definitely abnormal. I interpret the lung signs as probably due to compression of the lungs. There was no anemia. We have not initiated the photoelectric-cell technic at the Peter Bent Brigham so I pass that by. I congratulate you on your advanced scientific methods.

So far we have been just casting around for the scent. We have not struck the real trail of the fox, but here in the x-ray report we get a scent. X-ray study, in fact, frequently gives a very strong scent, not always of the beneficent variety. It is sometimes that of a little black and white animal that crosses the trail. I hope this will lead to the fox. If I may say so, these are excellent films, Dr. Holmes. I shall not insult the X-ray Department by saying that if we had better or more x-ray films we might make a better diagnosis. These films are quite adequate, and the written report is a marvel of completeness. There is a definite, sharply outlined, round mass in the posterior mediastinum behind the heart, pushing the esophagus backward so that the mass lies between the heart and the esophagus. It does not obstruct the esophagus, simply displaces it. So far as I can see, the mucosal markings in the esophagus are intact, so that presumably the mass does not arise from the mucous membrane of the esophagus. The statement that it showed a transmitted pulsation I take with a grain of salt. It is very difficult to tell whether a pulsation under the fluoroscope is transmitted or intrinsic, unless you can see both borders of the mass at the same time. If both borders expand simultaneously you can feel sure it is an intrinsic pulsation, except when there are two masses on either side of the pulsating aorta. Most of the statements in this x-ray report are facts, but this one is an impression or an opinion and we must consider it as such.

"Examination, including films in the horizontal and upright positions, showed no definite change in the shape of the mass by gravity." A very thin-walled cystic mass or collection of fluid might possibly show a change in shape when the patient changes from the upright to the prone or supine position.

"It moved markedly upward during the swallowing act." That is a very important statement and to me it means that the mass is closely applied to, or adherent to, or part of the esophagus itself. It moved upward during swallowing. It should be a part of the esophagus or at least very firmly adherent to it, or to the trachea. The esophagus was markedly flattened in the anteroposterior view and displaced backward in the lateral view. Another important fact is the abrupt change in the course of the esophagus which occurred at the upper edge of this round mass. The esophagus turned backward with a very acute angulation. Most of the mediastinal masses which are not part of the esophagus cause a more gradual curve

and do not have this acute angulation. This suggests that the mass was either in the esophageal wall or very firmly adherent to it.

The narrowing of the left bronchus accounts for the chief symptom, which was cough. You can see how markedly narrowed the left main bronchus is as it crosses over the upper left border of the round mass.

"There was a triangular area of marked homogeneous density along the left lower thoracic spine, which extended upward toward the region of the hilus." Here is the second mass, or shadow. Another mistake we make is in calling these masses. They really are shadows. This shadow fills the paravertebral space behind the heart. It is a very dense, homogeneous shadow, which we must relate to the round shadow above. The most probable guess would be an atelectatic collapsed left lower lobe. The other facts noted in the report (heart to left, fewer lung markings on the left) tend to confirm this.

What are the possibilities? The most frequent masses in the posterior mediastinum are enlarged lymph nodes from lymphoma, metastatic cancer or tuberculosis. I think we can rule out nodes because it is such a distinctly round mass; they would be more lobular. If they were tuberculous they might conceivably contain calcification. Primary carcinoma of the mediastinum is extremely rare, and I do not know of any primary malignancy that would give such a distinct round outline. Hydatid cyst is a possibility. It may occur as a distinct round mass in the posterior mediastinum. The majority of the ones I have seen have had linear areas of calcification in the wall when as big as this. Since there are no calcified areas I should tend to rule it out. A tumor of the heart or pericardium must be considered because the mass is intimately connected with the posterior surface of the heart. We can see no dividing line. We may have fibromas or fibromyxomas of the pericardium, of which I have seen two in the past two years. It most probably, though, is a tumor in the wall of the esophagus itself, not of the mucosa. It probably is not a carcinoma because the mucosal membrane is intact and because the mass is so large and so sharp in outline. The angulation, as I have mentioned before, is very definite evidence for a primary tumor of the wall of the esophagus. The moving upward on swallowing is also very definite evidence in favor of it. There must be a dozen reported varieties of tumor of the wall of the esophagus — osteochondroma, lipoma, myxoma, fibroma, fibroadenoma, leiomyoma and, frequently, particularly in children, the peculiar cysts that apparently are reduplications of the gastrointestinal tract. They have had a series at the Children's Hospital, and one may find anything histologically in that type of cystic tumor. Cartilage, due to the embryonic connection between the esophagus and trachea, is frequently found in these tumors.

I sum this up by saying the x-ray at least gives us a tally-ho on the quarry and shows a tumor or cyst, probably benign, and probably originating in the wall of the esophagus. The ones that get this big without giving further symptoms should be either one of these cysts due to reduplication of the gastrointestinal tract or a leiomyoma. We still have to explain the triangular shadow here, and I think that might be complete atelectasis of the lower lobe due to pressure of this mass on the left lower-lobe bronchus, a completely atelectatic left lower lobe. When you look at this chest film I think it is evident that there are fewer vascular markings around the left hilus than around the right. Normally these markings stand out more on the right, but this difference is more than we usually see. It would all fit in with an atelectatic left lower lobe.

There are a couple of mousetraps in this case. One is that the results of the Wassermann and Hinton tests are not mentioned in the abstract. When I find anything unusual, I always make the best interpretation possible and then put in parentheses, "syphilis must be excluded." Gumma is a possibility.

DR. BENJAMIN CASTLEMAN: Neither the Hinton nor Wassermann test was done.

DR. SOSMAN: That leaves a definite possibility of gumma. I shall put leiomyoma or cyst first and put in gumma as a dark horse. The last report is that the quarry has been sighted and the surgeon has been called in.

DR. J. H. MEANS: Do you think it could be a goiter?

DR. SOSMAN: I have never seen one as round and smooth and as low as that.

DR. MEANS: Dr. Churchill had a case like it that turned out to be goiter. There is a picture of it in my book. It rested on the right diaphragm, directly beside the heart. It was as round and smooth as could be. We thought it was a dermoid cyst, but it proved to be a goiter. I was interested in the note about swallowing because the trachea goes up and down. That might suggest substernal goiter. I am not offering that as a diagnosis, but I think it is a remote possibility.

Dr. Sosman: I have never seen one, but I doubt if it would cause acute angulation of the esophagus. That should mean something intrinsic in the wall of the esophagus.

Table 1. *Data on Five Cases of Mediastinal Cyst.*

Age	Sex	Symptom	Duration	Clinical Diagnosis	X-Ray Diagnosis	Operation	Histological Findings	End Result
yr.			yr.					
63	M	Epigastric pain	15	Tumor of pericardium	Malignant tumor of pericardium	Resection	No epithelial lining	Good
33	M	Pleurisy and cough	6	Mediastinal cyst	Mediastinal cyst	Drainage by marsupialization	Respiratory epithelium	Empyema and draining sinus
67	F	Upper abdominal pain and gas	20	Carcinoma of lung	Carcinoma of lung	Evacuation	No biopsy	—
34	F	Pleurisy	1/12	Mediastinal tumor	Neurofibroma or lymphoma	Resection	Respiratory epithelium	Good
42	M	Cough	2	Mediastinal cyst	Mediastinal cyst	Resection	No epithelial lining	Good

Clinical Diagnosis

Cyst of mediastinum, bronchiogenic.

Dr. Sosman's Diagnosis

Leiomyoma or benign cyst arising in the wall of the esophagus (gumma cannot be ruled out).

Anatomical Diagnosis

Congenital cyst of mediastinum.

Pathological Discussion

Dr. Castleman: I am sorry Dr. Churchill is not here, but I shall read his operative note:

> The left chest was opened through the bed of the eighth rib. The sixth and seventh ribs were cut between the transverse processes and the angles. The left lower lobe was found to be totally atelectatic. Projecting the lung forward, an incision was made over a cyst which presented between the aorta and the lung. A line of cleavage was found and developed. The cyst was slowly separated from the auricle anteriorly and the esophagus posteriorly. The muscular coat of the esophagus was spread out thinly over the tumor so that over a considerable area it was necessary to expose the undersurface of the mucous membrane. The most adherent part of the cyst was at the carina of the trachea, and it is possible that here was a fibrous cord representing the origin of the cyst. Early in the operation the wall of the cyst was punctured, and cloudy, yellowish fluid containing either fat droplets or cholesterol crystals was evacuated. The wound was closed without drainage.

The cyst was 8 cm. in diameter and contained yellowish mucoid material. The fact that the cyst was attached by a fibrous cord near the carina is very suggestive that it was congenital, forming during fetal life as the result of an imperfect closure of the communication between the trachea and esophagus. Another explanation of its origin is that it was an embryological rest pinched off from the trachea. Histologic study of the wall of the cyst shows only fibrous connective tissue. There is no respiratory or gastric epithelium, such as may be found in some cases. However, it is quite likely that pressure of the cyst contents had produced atrophy of the epithelium. This case makes the fifth mediastinal cyst that we have had in the past three years. Some of the clinical and pathological findings of these cases are presented in Table 1. It is interesting to note that in the three cases in which a resection was possible the postoperative course was excellent.

CASE 26292

Presentation of Case

A fifty-eight-year-old woman was admitted to the hospital complaining of weakness and epigastric gaseous distress.

The patient stated that stomach upsets had troubled her throughout her entire life. Even as a girl she remembered visiting a physician because of indigestion. At the age of thirty years, or twenty-eight years before admission, she suffered an acute attack of epigastric pain, occurring at night, associated with vomiting and loss of appetite, and recurring every day for about two weeks. There were no hematemeses or tarry stools, and the attacks were not associated with hunger or an empty stomach. They were relieved only by hot fomentations applied to the upper abdomen. These attacks of stomach distress, with frequent gaseous eructations, continued at irregular intervals throughout her life. The episodes were not known to have been associated with any food or bowel habits. Approximately six months before admission there appeared to have been a change in symptoms. At that time she experienced increasing weakness, faintness and dizzy spells, during which she felt as though she were going around in circles. This caused her to cease walking alone in the city. Gaseous distention

with frequent belching became more prominent, and she believed that she had passed, on a few occasions at least, tarry or black stools. Ten weeks before admission she arose early one morning to go to the toilet, but as she felt extremely weak and began to perspire profusely she returned to bed; a few hours later she passed a large black stool. She was too weak to sit erect. She was kept in bed for two days. Again a stool was passed which was black, and on examination by her physician it was found to contain blood. She was then admitted to an outside hospital, where she received an immediate blood transfusion and was placed on a milk-and-cream three-meal diet. The hemoglobin was found to be 22 per cent, the red-cell count 1,800,000. X-ray studies two weeks after admission demonstrated what appeared to be a posterior-wall gastric ulcer. Gastric analysis showed no free acid. She remained in bed for three weeks and improved symptomatically. However, on leaving the hospital for the first time she experienced severe, agonizing pain in the lower right mid-axillary region, accompanied by or associated with epigastric gaseous distention. Both distention and pain were relieved by belching. After hospital discharge she remained at home and gained weight rapidly, although she stated that she was completely anorexic. There was no vomiting or weight loss during the six-week interval before admission. The patient was treated with iron, vitamins, barbital, and Amphogel (an alumina gel) following each meal. Because the symptoms persisted she was referred to this hospital for further diagnosis and treatment. It was revealed that for many years the patient had experienced attacks of substernal constriction radiating to both arms. These attacks occurred in cold weather when she exerted herself by walking, particularly if she had just eaten a large meal, and were relieved by resting and by belching gas. She never experienced the discomfort in warm weather, and during the two or three years before admission had had no attacks, although her activity had continued about the same. There were no other cardiac symptoms.

The remaining family, marital and past histories were non-contributory.

Physical examination revealed a well-developed and well-nourished woman. The skin, tongue and mucous membranes were pale. Examination of the heart and lungs was negative. The blood pressure was 160 systolic, 90 diastolic. There was a slightly tender, round, apple-sized mass in the left central epigastrium, which moved slightly with respiration. The point of attachment could not be determined. There were no other palpable masses. The liver, spleen and kidneys were not palpated. The nails were spoon-shaped, and the hands and lower extremities were normal. Rectal and pelvic examinations were essentially negative.

The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,600,000 with 65 per cent hemoglobin (Tallqvist), a white-cell count of 5800 with 70 per cent polymorphonuclears, and a microcytic hypochromic smear, with marked variation in size, shape and hemoglobin content of the red cells, with many oval and tailed forms, but with no basophilia or nucleated red cells. The urine was negative. Frequent stool examinations were guaiac negative. The gastric analysis showed no free or combined acids either fasting or after alcohol or histamine; the specimens were guaiac positive and one was actually blood streaked.

Roentgenograms of the gastrointestinal tract revealed that the esophagus was normal. In the body of the stomach there was a large, oval, smooth, slightly lobulated mass over and around which the barium had to pass before it reached the antrum. The mass was 8 cm. long, was slightly movable and was attached to the left curvature of the stomach by a broad base. The pedicle was at least 5 cm. in diameter, the upper border being 2.5 cm. inferior to the cardiac orifice. The remainder of the stomach contained semisolid food particles but was otherwise negative. The pylorus opened readily, and the barium outlined a normal duodenum. A chest plate and an electrocardiogram were normal.

Gastroscopy showed in the body of the stomach, anterior to the gastroscope and somewhat below it as it lay against the posterior wall, a rounded, slightly nodular mass covered by smooth, normal-appearing mucosa. The entire tumor could not be well visualized, and although the area of the greater curvature was somewhat obscured by retained secretion, the impression was that of a non-ulcerative tumor lying below the mucous membranes, and presumably attached along the anterior wall and lesser curvature. There was thickening in the region of the antrum, and peristaltic waves were observed to stop in this region as they approached the pylorus. No ulceration or bleeding was observed.

On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Helen S. Pittman: May we see the x-ray films?

Dr. Aubrey O. Hampton: I think you can see the mass very easily (Fig. 1). It fills most of

the fundic portion of the stomach and is attached along the lesser curvature. It is smooth, and I do not believe you can tell whether the mucosa is intact or not, but in the adjacent stomach wall the mucosal folds are normal. Near the center

FIGURE 1.

of the shadow there is an indentation in the tumor outline about 1 cm. in diameter that suggests ulceration.

DR. PITTMAN: Was there normal peristalsis by x-ray?

DR. HAMPTON: There are two waves, not very deep. I think it would have been mentioned in the report if they were abnormal. The stomach does look dilated and rather atonic and does contain secretions or fluid. There is no evidence of previous gastric ulcer.

DR. PITTMAN: We have two clear-cut things given to us here — a hypochromic, microcytic anemia and a large tumor of the stomach. Probably the most important thing is the sequence of events in the development of these two conditions. I believe the tumor was benign and had been there for a long time. She had had stomach upsets practically all her life — at least twenty-eight years. It was at the age of thirty that she began to have occasional serious bouts and acute attacks of pain at night with vomiting, relieved by heat, and I am inclined to attribute these to the presence of the polyp or tumor, probably then of smaller size, in the stomach at that time. It seems to be attached too far up for it to have prolapsed through the pylorus. It is possible that she might have had superficial ulceration at that time, for the pain was more or less like ulcer pain coming on at night. She did have a good deal of vomiting with it, a circumstance which is not suggestive of ulcer.

The next point chronologically happened six months before admission, when there began to be a change in health. She was dizzy and weak — the first indication of blood loss or anemia. Ten weeks before admission she had gross blood loss; she was weak and perspired and soon after passed large black stools, at least twice. She was treated in another hospital on the assumption that she had an ulcer, although at that time it was found she had gastric anacidity. She went home and had very severe agonizing pain in the lower mid-axillary region. Whether she could have had intussusception or partial intussusception at that time I am not sure, but I am going to attribute the severe right-sided pain to the presence of the tumor of the stomach.

What about the tumor? I believe that statistically speaking the commonest type of benign gastric tumor, which this certainly was, at least in the beginning, is a myoma. It comprises about 60 per cent of all such tumors. I do not see that we have sufficient evidence from the report to suggest that it had undergone malignant degeneration. It was bleeding, but I think she perfectly well may have had ulceration on the surface of the tumor, or in the surrounding gastric mucosa which had been damaged by the presence of this large tumor in the stomach.

She had achylia, but this may accompany either a benign gastric tumor or hypochromic anemia. It is quite variable with the benign tumors as to whether or not there is significant change in the acidity of the gastric juice. I believe the fibro-adenomatous polyps are the ones which are most consistently accompanied by achylia, but statistically, as I have said, the myomas predominate as the benign tumors. Achylia occurs in about 60 per cent of cases of idiopathic hypochromic anemia.

As to the anemia, the underlying factor in hypochromic anemia of the idiopathic type is supposed to be a disturbance of gastric secretion, and she certainly had had plenty of cause for disturbance of the stomach by pressure of this tumor. She could have had this blood picture from bleeding, but I do not believe that I have ever heard of spoon-shaped fingernails following bleeding.

My diagnoses on this individual are that she had a long-standing benign tumor of the stom-

ach — a myoma or a fibroadenomatous polyp — and a microcytic, hypochromic anemia, secondary to long-standing gastric disease. The tumor had probably had ulceration in it at some time and may have undergone some malignant change, but there seems to be little evidence for the latter.

DR. THOMAS V. URMY: I can perhaps correct the impression about the gastroscopic examination relative to the peristaltic waves. They did not actually stop at the angulus. They were seen to pass down through the antrum, but the antrum seemed distorted by what appeared to be thickening of the wall and the waves were uneven. I got the impression that the wall was infiltrated. You do not often see peristaltic waves above the angulus during that type of examination. It was apparent from what I could see of the tumor that the mucous membrane was for the most part intact. However, I could not see the anterior surface because of the position of the gastroscope. There was no generalized gastritis which might explain the hemorrhage, but there had been plenty of time between the previous hospital admission and this one for acute erosions to have healed.

CLINICAL DIAGNOSIS

Sarcoma of stomach.

DR. PITTMAN'S DIAGNOSES

Benign tumor of stomach (myoma or fibroadenoma).

Microcytic hypochromic anemia, secondary to gastric disease.

ANATOMICAL DIAGNOSIS

Leiomyoma of the stomach.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: When this patient was operated on, the surgeon was rather puzzled by what he found. There was obviously a big tumor filling the cardia. A narrow segment of normal stomach intervened, and the entire antrum was markedly thickened, so much so that it felt very much like a scirrhous carcinoma, a linitis plastica of the stomach. The surgeon was afraid to remove merely the obvious tumor, which could easily have been resected, since he feared there might be a second malignant process in the pyloric region; so he did a virtually subtotal resection. The antral wall was about 1 cm. in thickness, but the thickening proved to be due purely to muscular hypertrophy. There was no tumor in this region, and no significant inflammatory infiltration. The most likely explanation, I think, is that this tumor of the cardia was sufficiently mobile so that the patient had very numerous and frequent bouts of intussusception with resulting pyloric obstruction and secondary hypertrophy of the antral and pyloric musculature. On the apex of the tumor, a shallow erosion was found corresponding in location to the one demonstrated by x-ray. It was very shallow, only a few millimeters in depth, and 1 cm. in diameter. That is very likely the spot from which the hemorrhages occurred, although she may have had erosions elsewhere which had healed.

Regarding the peristaltic waves, I think a stomach wall as thick as that probably would not work very actively. It would almost impede its own action.

The tumor on microscopic examination was a benign leiomyoma. The sections were absolutely indistinguishable from those of an ordinary fibroid of the uterus, and I think there is no doubt that she had had the tumor at least throughout the whole period of her symptoms and probably even longer.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

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MATERIAL for early publication should be received not later than noon on Saturday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PREMEDICAL EDUCATION

PRESIDENT Conant,* of Harvard University, has recently suggested that matriculants for the medical schools of this country be chosen, at least in part, at the end of their freshman year in college. The idea is not a new one. A somewhat similar method of selection has been in vogue in England and on the Continent for many years. As applied to the United States, however, the proposal is a novel one and deserves both careful consideration and meticulous scrutiny. It is argued that, by and large, the scholastic record in a graduate school is a rather true reflection of a student's attainments in preparatory school and in his freshman year in college. If this be true, and if a sufficiently large number of students have, before the end of their freshman year, a clear and decisive intention of entering the profession of medicine, it may further be argued, as Mr. Conant has, that guidance by a joint committee from the college and medical school faculties during their remaining three college years might be of great advantage.

It is true that high honor men in the preparatory school and in the freshman year at college will probably continue to do at least creditable and possibly honor work in medical school. From such a group, those who intended to enter medical school could without doubt be chosen with no greater margin of error than now obtains under the system whereby men are selected on the basis of three or four years of college. Such is the case in England and on the Continent; however, certain fundamental differences exist. In England, those who enter the medical profession come almost exclusively from the intellectual and highly educated classes, and British matriculants in medicine, owing to the competitive system of the so-called "public schools," probably have far more factual knowledge and have studied more intensively in their teens than have the majority of their American cousins. In this country, on the other hand, there is a large group of students who, lacking cultural background, are slow to mature intellectually and do not find themselves scholastically until toward the end of their college career. From this group of men come some of America's ablest physicians, and to choose the majority of applicants for medical school at the end of the freshman year would almost certainly exclude a number of excellent men.

The suggestion that a joint committee from the medical school and the college guide those chosen from the freshman class also has its drawbacks as well as its advantages. Theoretically, the man who intends to enter a research career could have his course so planned as to fit him well for his subsequent work, and he who desires to become a practitioner of medicine could have outlined for him a broad educational course, including the minimum requirements in premedical sciences. In actuality, however, it is doubtful whether many freshmen, even if they have decided on a medical

*Conant, J. B.: College education for the future doctor. *Federation Bull.* 25:269-277, 1939.

career, know which of the many branches of medicine they wish to enter. Indeed many fourth-year medical students are still uncertain. The special guidance might, therefore, prove to have been along unsuitable lines.

Perhaps a compromise between the old scheme and the new would accomplish the most. Let the medical schools choose from the freshman class a limited number of honor men who are determined to enter medicine and let these few be carefully guided for the next three years. Let the majority of medical students be chosen as heretofore at the end of their college careers.

What college courses should be recommended for the majority? Certainly the minimum premedical science and language requirements should be covered. Without these no man can take full advantage of the present medical curriculums. Beyond this it would seem wise to allow, in fact to urge, each prospective student of medicine to follow his own scholastic bent, regardless of whether his interest lay in history, languages, fine arts or science; such diversification may later prove to be of distinct value in view of the complexity of work in medicine and the variety of opportunity in the medical field. If the student on entrance to college has no specific intellectual interest, it would probably be wise for him to concentrate on the premedical sciences, — chemistry, biology, physics, embryology, comparative anatomy and the like, — for such a man is likely to have scholastic difficulties in medical school and the more time he has spent on purely medical subjects the better he is likely to fare.

FROZEN FOOD

THE frequency with which home cooking is extolled throughout the land should have long ago brought forth some impelling reasons why it is superior to the sort of cooking we might otherwise expect to find in our restaurants and bakeshops. It is apparently just one of those things that is so. The home preservation of food has not been correspondingly free from suspicion, however. It has been scientifically compared with the various commercial processes, usually to its detriment, and has been unable to establish for itself any convincing point of superiority.

There are three primary methods of preserving food: to sterilize it by the application of heat, as with the pasteurizing processes, with subsequent protection against infection; to cure it for storage by a salting (corning), drying or smoking process; and to inhibit bacterial and fermentive changes by chilling or freezing while still fresh. Technical advantages and disadvantages attach themselves to all these methods.

The development of artificial refrigeration has given a recent stimulus to explore the possibilities of this method. For the best results extremely low temperatures are necessary. Rapid freezing is desirable with many foods in order to prevent the formation of ice crystals which pierce the delicate cell walls, thus causing leakage with consequent change of texture and loss of flavor. Fruit and vegetable cells are more vulnerable in this respect than those of animal products, which are elastic and less easily ruptured. The usual temperature range for rapid freezing is from 0 to –40°F.

A tremendous growth in the frozen food industry has taken place in the past few years. In 1938 the production was close to half a billion pounds. A report by Rose* summarizes the temperatures, types of process, selection of foods and preservation of nutritive values, and gives fifty odd references to the literature in this field of growing importance. On the basis of this report the Council on Foods of the American Medical Association has voted to give consideration to quick-frozen vegetables and fruits with a view to inclusion in the list of accepted foods.

The many advantages of this method of food preservation are dependent on a rather complicated system of transportation and storage, for refrigeration must be maintained throughout, from the original freezing to the purchase by the consumer. This means refrigerated railway cars, trucks, lockers and display cabinets, as well as home facilities provided the food is to be kept for any period of time. Strawberries in December and oysters in July may yet become commonplace!

*Rose, M. S.: The effect of quick freezing on the nutritive values of foods. *J. A. M. A.* **114**:1356-1361, 1940.

MEDICAL EPONYM

Chvostek's Sign

In a "Beitrag zur Tetanie [Contribution to the Study of Tetany]" published in installments in the *Wiener medizinische Presse* (**17**: 1201–1203, 1225–1227, 1253–1258 and 1313–1316, 1876), Franz Chvostek (1835–1884), of Vienna, first mentioned the characteristic sign which is now known by his name. A portion of the translation follows:

> In my case the mechanical irritability of the nerves and muscles was enormously increased, so that even the lightest touch over the nerves of the extremity elicited a twitching of the innervated muscles. . . . The mechanical irritability of the branches of the facial nerve and the muscles supplied by it was also markedly increased. This increase in mechanical irritability gradually lessened with the subsidence and after cessation of the spasms, but never entirely disappeared. . . .
>
> So far as I know, this increased mechanical irritability has never been mentioned before.

R.W.B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Fatal Influenzal Bronchopneumonia

Mrs. M. S., a thirty-nine-year-old para V, was seen at home on February 24, 1923, with a very bad cold and a bad headache. At this time she was three weeks from term. She was advised to go to the hospital but refused to do so. The temperature was 101°F., and the lungs were normal.

The patient's family and past histories were non-contributory. The previous pregnancies had been normal and uneventful. Catamenia began at thirteen and were regular, with a twenty-eight-day cycle. The last period began on June 8, 1922, making the expected date of confinement March 15.

The patient was first seen in the office on January 9. At this time she weighed 120 pounds. Examination showed that the heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The blood pressure was 120 systolic, 60 diastolic. There was no edema. The uterus was consistent in size with her dates, with the fetal heart heard in the left lower quadrant. Vaginal examination showed a cystocele; the cervix was soft and not taken up.

On February 20, four days before the home visit, the patient was seen in the office. She had no symptoms. The weight was 122 pounds, and the blood pressure 128 systolic, 60 diastolic. The vertex was presenting.

On February 25 she entered the hospital in labor, the membranes having ruptured spontaneously. The temperature was 101°F.; she looked very badly, and the respirations were rapid. She had a very easy, normal delivery under gas. The baby was a male weighing 6 pounds, 2 ounces, and survived.

On February 26 the patient was seen in consultation by an internist. At this time she showed signs of acute respiratory infection, without any demonstrable involvement of the lungs. She was moderately toxic but began to improve under treatment; however, the next afternoon she became more toxic and complained of pleural pain in the right chest. The respirations became more rapid, and there were pleural rubs at both bases, without any signs of consolidation.

On February 28 she showed signs of diffuse fluid in the pleural cavities. The white-cell count was 4400, and she presented a typical picture of influenzal bronchopneumonia. She was again seen in consultation, but she became progressively worse, the white count rising to 6800 on March 1, and died early in the morning of March 2.

Comment. This case illustrates the extreme severity of certain cases of influenzal pneumonia. The disease precipitated premature labor, and although the lungs were not hampered by the physical burden of a full-term uterus, the disease progressed rapidly to death. Today chemotherapy would be tried, although its value in influenzal pneumonia has yet to be proved. This patient was advised to go to the hospital the day she was seen at home. This she refused to do, although it is doubtful that, if she had, the outcome would have been different.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

DEATHS

COTTER — Timothy F. Cotter, M.D., of Haverhill, died July 3. He was in his fifty-ninth year.

Born in Somerville, he attended Boston College High School and Georgetown University. He received his degree from Baltimore Medical College in 1906 and served his internship at the Haverhill City Hospital.

Dr. Cotter was a member of the Massachusetts Medical Society and the American Medical Association.

His sister survives him.

VIVIAN — WILLIAM J. VIVIAN, M.D., of Northport, L. I., New York, died June 10. He was in his fifty-seventh year.

Dr. Vivian received his degree from Dartmouth Medical School in 1912. He was a member of the Massachusetts Medical Society, the American Medical Association, the American Psychiatric Association and the New England Society of Psychiatry.

MISCELLANY

BRITISH EMBASSY REGISTERING AMERICAN PHYSICIANS FOR SERVICE WITH GREAT BRITAIN

The British Embassy is registering the names of American physicians who volunteer for service in the United Kingdom in the treatment of casualties so as to have available a list of men who may be called on if the need arises. The statement is made that these men are required mainly for the treatment of civilian casualties and that there is no question of enrolling these men in the medical services of the war forces.

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ARTICLES ACCEPTED BY THE COUNCIL ON PHARMACY AND CHEMISTRY, AMERICAN MEDICAL ASSOCIATION

To the Editor: In addition to the articles enumerated in our recent letter the following have been accepted:

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- Liver Extract — Abbott (powder), in capsules
- Liver Extract-Injectable, U.S.P., Abbott, 5 U.S.P. units
- Liver Extract-Injectable, U.S.P., Abbott, 10 U.S.P. units

Arzol Chemical Co.
- Arzol Ferric Swabs

Calco Chemical Co., Inc.
- Sodium Sulfapyridine Monohydrate — Calco

Cutter Laboratories
- Pollen Extracts — Cutter (Acacia; Alder; Alfalfa; Alkali Rye Grass; Almond; Annual Blue Grass; Aspen; Barley; Bent Grass; Birch, Bract Scale; Brome Grass; Broncho Grass; Canada Blue Grass; Chapparal Broom; Cheat Grass; Chrysanthemum; Clover; Coreopsis; Cosmos; Cultivated Rye; Curly Dock; Dahlia; Dandelion; Date; Deodar Cedar; Elm; English Walnut; Eucalyptus; False Coastal Ragweed; Field Oats; Field Wheat; Goldenrod; Greasewood; Hops; Incense Cedar; Koehler's Grass; Locust; Mesquite; Mexican Tea; Monterey Cypress; Mountain Sagebrush; Mustard; Pasture Sagebrush; Pecan; Perennial Rye Grass; Pickleweed; Poverty Weed; Prairie Sagebrush; Privet; Quack Grass; Rabbit Brush; Rose; Salt Grass; Shasta Daisy; Sheep Sorrel; Slender Wheat; Southern Ragweed; Spearscale; Spiny Amaranth; Squirrel Tail; Sugar Beet; Sunflower; Sweet Vernal; Sycamore; Tall Oat Grass; White Valley Oak; Willow; Yellow Pine)

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- Diphtheria Toxoid, Refined, Alum Precipitated (1 immunization, 2 doses, 1 cc. each)
- Diphtheria Toxoid, Refined, Alum Precipitated (10 immunizations, 2 doses, 1 cc. each)

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- Antipneumococcic Serum, Concentrated (Pneumococcus Antibody Globulin, Types I and II) — Mulford, 20,000-unit package
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  - Tablets Atabrine Dihydrochloride, 0.1 gm. (1½ gr.)
  - Tablets Atabrine Dihydrochloride, 0.05 gm. (¾ gr.)
  - Ampules Atabrine Dihydrochloride Powder, 0.2 gm., with ampules, 10-cc. size, sterile distilled water.

John Wyeth & Brother, Inc.
- Silver Picrate Jelly — Wyeth, 0.5 per cent
- Soluble Trituration Silver Picrate, 20 per cent, with boric acid, 80 per cent
- Sulfapyridine — Wyeth
  - Tablets Sulfapyridine — Wyeth, 0.5 gm. (7.7 gr.)

The following articles have been accepted for inclusion in the list of articles and brands accepted by the Council but not described in N.N.R. (*New and Nonofficial Remedies*, 1940, p. 560):

Endo Products, Inc.
- Ampoules Calcium Chloride Solution — Endo

Lakeside Laboratories, Inc.
- Ampules Magnesium Sulfate — Lakeside, 25 per cent, 2 cc.
- Ampules Magnesium Sulfate — Lakeside, 10 per cent 10 cc.
- Ampules Magnesium Sulfate — Lakeside, 10 per cent, 20 cc.

PAUL NICHOLAS LEECH, *Secretary.*

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THE "DISCOURAGED STAGE" IN THE CONVALESCENCE FROM INDUSTRIAL INJURIES

To the Editor: Last winter, owing to the hurricane, I had many fallen trees to be cut up and sawed. I happened to have three patients on whom I had operated for rupture of the supraspinatus muscle who were conva-

lescing. I employed these men, supervising their work to make sure their shoulders were not overused and letting them take their own time. I paid them only very small wages, but they seemed glad to help me all they could in return for what I had done for them. It was a great pleasure to me to see the rapid improvement in morale, as well as in general physical condition, which took place. They learned that they not only could work again, but that their work was of more value than the payment they received. They knew that they were giving me something. The experiment was so successful that I have decided to try a similar one on a larger scale.

Everyone familiar with the affairs of injured industrial employees will recognize what I mean by the "discouraged stage" of convalescence following an injury. Almost any patient bears up well when his trouble is acute, for in most cases the acute stage is over in a month and improvement is visible from day to day — certainly as seen from week to week. Often, however, progress is slower. In certain conditions, especially those following injuries to the back, knees and shoulder, improvement may be so slow that it is not recognizable from week to week. It is then that the "discouraged stage" begins. The loss in morale may be greater than any physical gain. The patients get to think that they will never be able to work again, and worry exaggerates their symptoms. Month by month they lose in general condition, not only from lack of use for their muscles but also from lack of nutrition, if their compensation is not adequate for the size of their families. As such injuries often occur in the latter half of life, the age factor looms in this discouragement. Not only do their tissues degenerate more rapidly than in youth, but their optimism also. They need work more than local physiotherapy.

Under modern industrial conditions the jump from idleness to full-time work is too abrupt. There should be some opportunity for convalescent employees to "harden up" before resuming their regular trade hours. They should be given opportunity "to take their own time," when they first return to work.

My answer to this problem is that in most cases there is almost a whole man to make use of, even if he cannot give full use of the injured part. An employee with an injured shoulder can run errands, carry a pail of water, throw a switch, lift one end of a log, keep accounts and do a hundred other things without abusing his shoulder. And this is true in the case of many other disabilities. Obviously work should be selected which they can do, and this should be the primary consideration of the organizations that employ them.

I therefore propose to organize a business — perhaps better called a therapeutic business — in which I can use convalescents in the "discouraged stage" at very low wages.

It so happened that the three patients mentioned above presented three different, although in most respects similar, medicoeconomic problems. All three were married men with families of from four to nine children dependent on them for support. The economic differences were that one was a private patient, one a compensation case and the third a charity patient.

The private patient was a laboring man on whom I had operated for rupture of the supraspinatus muscles in both shoulders and obtained good results. After his recovery he got his old job back and worked for me on off days until he had canceled his bill.

The compensation case was that of a painter who had not only torn the supraspinatus muscle but the infraspinatus and teres minor muscles as well. An excellent but not a perfect result was obtained. The insurance company paid me for his care, and I paid him a small amount for his work. Ultimately the insurance company made a generous settlement with him, as he had shown his willingness to do the best he could with a somewhat impaired arm.

The third patient, a carpenter, was a charity case at a public hospital. An operation restored his ability to work without pain. His family of ten was on relief, and so I paid him a small amount, for although he was not in a condition to do regular work yet he was ready and willing to do anything he could. He grew steadily stronger and by now has done so much for me that I feel he has repaid me for the operation and for the little I have paid him.

Thus in all three cases I have been paid and paid cheerfully. In the second and third cases I have been able partially to pay the patients for their services, also. They all have a realization that they have worked for me for wages that were less than they earned and deserved. I wish to cultivate this realization, for to make them realize that their work is of value is a part of my therapeutics. Before I had operated on them, I believe that all three had the impression that they were useless and perhaps burdens to their families.

This frame of mind in laboring men is most pitiable. Accustomed to daily physical work, they have an indescribable restlessness. One hears them say, "It seems as if I would go crazy without anything to do all day." I have heard this phrase used again and again by patients with injured shoulders, and often in the case of other injuries which cause only partial incapacity, but prevent getting jobs. Society should make some provision for these cases. There are few impaired men whose work is not worth a dollar a day, and many whose work is worth more, even when they take their own time in doing it. It is hard enough for able-bodied laboring men to get jobs and practically impossible for these convalescents, especially if they are elderly. Yet, as in the case of this carpenter, their experience itself has a value, and their advice alone is worth much to the ordinary man, who, for instance, is trying to do a carpentering job. I think I could build a house myself if this carpenter sat by and told me what to do next, and how to do it!

As I have now retired from the active practice of general operative surgery I propose to devote my remaining professional life to this problem, especially so far as it concerns patients with lesions of the shoulder, in the diagnosis and treatment of which I am especially interested.

No patient will be too poor, if he will pay with what work he is able to do during or after his treatment. There are many patients attending charitable hospitals who could benefit from this plan. Industrial insurers might profit by the opportunity to send patients to be hardened up before they return to full-time work, and some cases that are on relief might be rehabilitated. In certain penniless cases I might advance a payment of a dollar a day.

I own 90 acres of pasture and woodland just over the Hingham line in Norwell, Massachusetts. This land furnishes an abundance of light work, such as cutting out wild-cherry trees, burning brush and trimming dead branches, as well as heavier work, such as chopping, sawing and stacking wood from trees felled by the hurricane. It is obvious that under present economic conditions I could not hire labor at the usual rates to cut wild-cherry trees, saw off dead branches and so forth. The amount of increased value of the land would not justify the expense. On the other hand, if I could obtain

the labor for nothing, undoubtedly I should eventually obtain a somewhat better price for the land. *But* I do not plan to get the labor for nothing — I exchange for it advice, which should have value from the many years I have devoted to the study of shoulder conditions and the time which it will take to examine these patients and to supervise their work. I do not plan to have this project a philanthropy, but a fair exchange of labor. If I am successful, some such plan may be adopted by the State for individuals partially incapacitated by injuries other than those involving the shoulder. There is much idle unimproved land in this state, and many idle unimproved convalescents.

A co-operative spirit must be shown by the patients, and in turn I shall study out ways in which they can use the rest of their muscles without abusing their shoulders, and set them at work that they can see will benefit me, as well as themselves.

E. A. Codman, M.D.

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Boston.

REPORT OF MEETING

HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on March 12, with Dr. Soma Weiss presiding.

The first case presented was that of a forty-five-year-old man who four months before had had upper abdominal pain for one to two hours with no chills, fever, jaundice or nausea. An intravenous cholangiogram revealed "sand" in the gall bladder, and an operation was performed. This was a difficult procedure; a mass of induration at the ampulla was encountered, and common-duct exploration was not carried out because of the patient's precarious condition. He was discharged improved, only to return after increasingly severe episodes of the same nature, except that they were accompanied by jaundice and vomiting. Laboratory data revealed a prothrombin time of 18 seconds, an icteric index of 33 and a blood cholesterol of 354 mg. per 100 cc. The findings were otherwise essentially normal. Ten milligrams of vitamin K was given preoperatively. At operation a similar mass of inflammatory tissue was found obstructing the ampulla and the abdomen was closed after the insertion of a catheter into the common bile duct. Dr. Elliott C. Cutler observed that the rapid loss of vitamin K during operations, even those of a minor nature, has not been well explained.

The second case was that of a forty-nine-year-old woman who developed successively headache, anorexia and jaundice about five months after the institution of arsphenamine therapy for syphilis. Nausea and vomiting were experienced in the middle of the first course of arsphenamine; thus Mapharsen was substituted, with relief of the vomiting. This in turn was replaced by Bismarsen intramuscularly because of the persistent nausea; finally Bismarsen was superseded by bismuth subsalicylate when local soreness developed. On admission two days after the onset of jaundice, the icteric index was 60, and the prothrombin time and all other data were within normal limits. Treatment consisted of daily intravenous injections of 2 liters of glucose until oral feeding could be tolerated. The icterus remained at the initial level for about three weeks before starting to taper off, while the prothrombin time remained normal throughout.

Dr. Weiss reminded the audience that acute hepatitis as a complication of antisyphilitic therapy is fast disappearing. He stated that early reactions should be heeded as a warning of impending or subsequent liver damage, the symptoms of which may appear only after months. Recovery should be complete if proper supportive measures are carried out. Dr. Weiss emphasized how difficult it is to predict prolongation of the prothrombin time despite clinical evidence of severe liver damage.

The first speaker of the evening was Professor Louis F. Fieser, of Harvard University, who discussed "The Chemistry of Vitamin K." He recounted the work of Dam, Almquist and Doisy, who a year ago independently isolated the vitamin from alfalfa. The characteristic ultra-violet absorption spectrum of the yellow oil was reported, and Doisy described the probable chemical structure, which he arrived at by careful degradation experiments. He concluded that the basic structure was a quinone radical with a long side chain. He computed that vitamin K_1 should contain about twenty carbon atoms, and vitamin K_2 about thirty.

Dr. Fieser, from a comparison of absorption spectrums, deduced that the fundamental compound was a naphthoquinone and probably had alkyl groups in the 2- and 3-positions. Knowing of several such naturally occurring compounds in which isoprenoid radicals were involved, Dr. Fieser considered what combination of a naphthoquinone radical with these alcohols could give the necessary number of carbon atoms and double bonds. This line of reasoning gave the right answer for vitamin K_1 and approached that for K_2, as it subsequently turned out.

By varying the technic of synthesis, Dr. Fieser was able within a few months to make 2-methyl-3-phytyl-1, 4-naphthoquinone, which proved by bioassay and absorption spectrums to be identical with the vitamin K_1 extracted from alfalfa. The compound was a clear yellow liquid completely insoluble in water and sensitive to light and alkali, but otherwise chemically inert. A characteristic color reaction occurs when an alcoholic solution is treated with alkali, but this was not considered satisfactory as the basis of an assay method because the brilliant purple quickly fades to a dull red.

It was observed that related quinone compounds had a biological antihemorrhagic activity as assayed in deficient chicks. The most potent of these was 2-methyl-1, 4-naphthoquinone, which proved to be three times as potent as the pure vitamin, but also somewhat more toxic in very large doses. This compound is utilized in the synthesis of vitamin K_1 in vitro, and Dr. Fieser postulated that it may occur in vivo, especially since its molecular weight is about one third and its activity about three times that of the complete vitamin, according to chick assay.

Dr. Fieser described the extensive work on various naphthoquinone derivatives in an attempt to correlate structure and function. Activity was found to occur in those compounds having one long chain in either the 2- or 3-position and up to a certain point was roughly proportional to the length of this alkyl group. Long carbon chains in both positions rendered the compound inactive, and the addition of an ethyl rather than a methyl group in the 2-position reduced the biological activity a thousandfold. Alkylation of the non-quinonoid ring inactivated the compound. The cyclic oxide of 2-methyl-1, 4-naphthoquinone and that of vitamin K_1 itself were found almost as active as the parent product. This was considered significant because of the greater ease of keeping and handling these stable compounds. In an attempt to make a water-soluble substance, work on the esters of the hydroquinones was carried out, and the so-

dium sulfuric ester of 2-methyl-1, 4-naphthohydroquinone was found on preliminary bioassay in chicks to be equivalent to vitamin K_1.

Observations on the clinical use of synthetic vitamin K_1 and associated compounds were reported by Dr. Arnold M. Seligman, of the Beth Israel Hospital. As an introduction, he enumerated the factors involved in hypoprothrombinemia: the absence of the vitamin from the diet as seen in the newborn and in chicks; the absence of bile from the gastrointestinal tract; the lack of a normal intestinal mucosa for absorption; and severe liver damage. Clinical conditions corresponding to each of these groups were mentioned: hemorrhage disease of the newborn; obstructive jaundice or a biliary fistula; extensive intestinal resections or sidetrackings, ulcerative colitis, celiac disease and sprue; and any liver disease, such as cirrhosis. Factors which may increase the severity of an underlying deficiency include hemorrhage, the exudation of fibrin as in pneumonia, sepsis or repair, increased liver damage, the vomiting of bile and the combination of surgery and anesthesia.

Dr. Seligman explained how the prothrombin time (Quick) is not notably affected until the blood-prothrombin concentration reaches approximately 40 per cent of normal and does not increase markedly until the blood level reaches 25 to 15 per cent.

The synthetic vitamin was found to produce a satisfactory lowering of the prothrombin time when administered orally together with bile, but the effect of a single dose was not lasting. In the search for an intravenous method of using the water-insoluble compound to obtain a longer duration and to obviate the necessity of giving bile, Dr. Seligman found that a solution of 10 mg. in absolute ethyl alcohol could be permanently suspended in nonparticulate form in a liter of 10 per cent glucose solution. This solution was found under comparable situations and in minimal dosages to produce greater, more rapid, and more lasting decreases of prothrombin time than either the sodium sulfuric ester or 2-methyl-1, 4-naphthoquinone. When moderately large amounts were administered intravenously, all produced a fall of the prothrombin time within a few hours to normal limits, which persisted for varying periods.

Dr. R. M. Kark reported that similar results had been obtained in obstructive jaundice at the Boston City Hospital by the intravenous route but that intramuscular injections produced effects which, although produced more slowly, lasted for five to six days. He also observed that attacks of cholangitis in such conditions prevent the effective utilization of the vitamin and that operations should not be performed during such periods of stress. Other instances of failure to affect the prothrombin time with vitamin K had been noted in cases of acute yellow atrophy, disseminated carcinomatosis and chronic liver disease.

NOTICES

AN ADDITIONAL STUDY TO EVALUATE ORIGINAL SEROLOGIC TESTS FOR SYPHILIS

More than five years ago the Committee on Evaluation of Serodiagnostic Tests for Syphilis, in co-operation with the United States Public Health Service, conducted a study to evaluate original serologic tests for syphilis or modifications thereof in the United States. The results of this study were published shortly after the investigation was completed (*J. A. M. A.* **104**:2083-2087, 1935).

Consideration is now being given by the committee to the organization of a second evaluation study of original serologic tests for syphilis or modifications thereof within the next year. If the need for an investigation of this kind seems to justify the cost, invitations will be extended to the authors of such serologic tests who reside in the United States or who may be able to participate by the designation of a serologist who will represent them in this country. The second evaluation study will be conducted utilizing methods comparable to those employed in the first (*J. A. M. A.* **103**:1705-1707, 1934).

Serologists who have an original serologic test for syphilis or an original modification thereof and who desire to participate in the second evaluation study should submit their applications not later than October 1, 1940. The applications must be accompanied by a complete description of the technic of the author's serologic test or modification. All correspondence should be directed to the Surgeon General, United States Public Health Service, Washington, D. C.

SOCIETY MEETINGS AND CONFERENCES

September 2–6 — American Congress of Physical Therapy. Page 862, issue of May 16.

October 6–11 — Annual meeting of Eye and Ear Specialists. Page 81, issue of July 11.

October 8–11 — American Public Health Association. Page 655, issue of April 11.

October 11, 12 — Pan-American Congress of Ophthalmology. Page 898, issue of May 23.

October 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Page 938, issue of May 30.

October 21 — American Board of Internal Medicine. Page 369, issue of February 29.

January 4, 1941 — American Board of Obstetrics and Gynecology. Page 1064, issue of June 20.

April 21–25, 1941 — American College of Physicians. Page 1065, issue of June 20.

District Medical Society

MIDDLESEX NORTH

July 31.
October 30.

BOOK REVIEW

Jewish Contributions to Medicine in America: From Colonial Times to the Present. By Solomon R. Kagan, M.D., foreword by Prof. James J. Walsh. Second edition — revised and enlarged. 8°, cloth, 792 pp., illustrated. Boston: Boston Medical Publishing Co., 1939. $3.50.

The first edition of this book, published in 1934, covering the lives of Jewish physicians from 1656 to date, was reviewed in the June 20, 1935, issue of the *Journal*. At that time, it was pointed out, "We have reason to be extremely grateful to the author and the publisher and to all whose labors have made possible the compilation and publication of this admirable contribution to the history of medicine in America." Dr. Kagan has now re-published his volume and added about 250 pages, with a new index, bringing the subject up to date. It is an invaluable reference tool to librarians and in addition will be of interest to all physicians as a sound book for their library. The book, moreover, gives an excellent idea of the extensive and valuable contributions made by Jewish physicians to medicine in America. It is divided into sections: medicine; neurology and psychiatry; dermatology and syphilology; surgery; otolaryngology and ophthalmology; hygiene and public health; and others. Thus, one can readily find a list of physicians who worked or are working in any special field. The book is well printed and published, and this revised and enlarged second edition is a distinct contribution to medical history.